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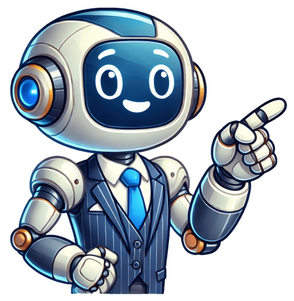

Vitamin used in animal cell metabolism This article is about the family of vitamers. For individual forms, see hydroxocobalamin, cyanocobalamin, methylcobalamin, and adenosylcobalamin. "B12" and "Cbl" redirect here. For other uses of B12, see B12 (disambiguation). For the musical group, see Carbon Based Lifeforms. Pharmaceutical compound Vitamin B12General skeletal formula of cobalaminsStick model of cyanocobalamin (R = CN) based on the crystal structure[1]Clinical dataOther namesVitamin B12, vitamin B-12, cobalaminAHFS/Drugs.comMonographMedlinePlusa605007License data US DailyMed: Vitamin_b12 Routes ofadministrationBy mouth, sublingual, intravenous (IV), intramuscular (IM), intranasalATC codeB03BA01 (WHO) Legal statusLegal status UK: OTC US: OTC Pharmacokinetic dataBioavailabilityReadily absorbed in the distal half of the ileum.Protein bindingVery high to specific transcobalamins plasma proteins.Binding of hydroxocobalamin is slightly higher than cyanocobalamin.MetabolismLiverElimination half-lifeApproximately 6 days(400 days in the liver).ExcretionKidneyIdentifiers IUPAC name α-(5,6-Dimethylbenzimidazolyl)cobamidcyanide CAS Number68-19-9PubChem CID184933DrugBankDB00115ChemSpider10469504UNIIP6YC3EG204KEGGD00166ChEMBLChEMBL2110563Chemical and physical dataFormula$C_{63}H_{88}CoN_{14}O_{14}P$Molar mass1355.388 g·mol−13D model (JSmol)Interactive image SMILES NC(=O)C[C@@]8(C)[C@H](CCC(N)=O)C=2/N=C8/C(/C)=C1/[C@@H](CCC(N)=O)[C@](C)(CC(N)=O)[C@@](C)(N1[Co+]C#N)[C@@H]7/N=C(C(\C)=C3/N=C(/C=2)C(C)(C)[C@@H]3CCC(N)=O)[C@](C)(CCC(=O)NCC(C)OP([O-])(=O)O[C@@H]6[C@@H](CO)O[C@H](n5cnc4cc(C)c(C)cc45)[C@@H]6O)[C@H]7CC(N)=O InChI InChI=1S/C62H90N13O14P.CN.Co/c1-29-20-39-40(21-30(29)2)75(28-70-39)57-52(84)53(41(27-76)87-57)89-90(85,86)88-31(3)26-69-49(83)18-19-59(8)37(22-46(66)80)56-62(11)61(10,25-48(68)82)36(14-17-45(65)79)51(74-62)33(5)55-60(9,24-47(67)81)34(12-15-43(63)77)38(71-55)23-42-58(6,7)35(13-16-44(64)78)50(72-42)32(4)54(59)73-56;1-2;/h20-21,23,28,31,34-37,41,52-53,56-57,76,84H,12-19,22,24-27H2,1-11H3,(H15,63,64,65,66,67,68,69,71,72,73,74,77,78,79,80,81,82,83,85,86);;/q;;+2/p-2/t31?,34-,35-,36-,37+,41-,52-,53-,56-,57+,59-,60+,61+,62+;;/m1../s1 YKey:RMRCNWBMXRMIRW-WYVZQNDMSA-L Y Vitamin B12, also known as cobalamin, is a water-soluble vitamin involved in metabolism.[2] One of eight B vitamins, it serves as a vital cofactor in DNA synthesis and both fatty acid and amino acid metabolism.[3] It plays an essential role in the nervous system by supporting myelin synthesis and is critical for the maturation of red blood cells in the bone marrow.[2][4] While animals require B12, plants do not, relying instead on alternative enzymatic pathways.[5] Vitamin B12 is the most chemically complex of all vitamins,[6][2][7] and is synthesized exclusively by certain archaea and bacteria.[8] Natural food sources include meat, shellfish, liver, fish, poultry, eggs, and dairy products.[2] It is also added to many breakfast cereals through food fortification and is available in dietary supplement and pharmaceutical forms.[2] Supplements are commonly taken orally but may be administered via intramuscular injection to treat deficiencies.[2][6] Vitamin B12 deficiency is prevalent worldwide, particularly among individuals with low or no intake of animal products, such as those following vegan or vegetarian diets, or those with low socioeconomic status.[9] The most common cause in developed countries is impaired absorption due to loss of gastric intrinsic factor (IF), required for absorption.[10] A related cause is reduced stomach acid production with age or from long-term use of proton-pump inhibitors,[11] H2 blockers, or other antacids.[12] Deficiency is especially harmful in pregnancy, childhood, and older adults. It can lead to neuropathy, megaloblastic anemia, and pernicious anemia,[2][13] causing symptoms such as fatigue, paresthesia, cognitive decline, ataxia, and even irreversible nerve damage. In infants, untreated deficiency may result in neurological impairment and anemia.[2] Maternal deficiency increases the risk of miscarriage, neural tube defects, and developmental delays in offspring.[14] Folate levels may modify the presentation of symptoms and disease course. Vitamin B12 is a coordination complex of cobalt, which occupies the center of a corrin ligand and is further bound to a benzimidazole ligand and adenosyl group.[15] Several related species behave similarly to function as vitamins. This collection of compounds is sometimes referred to as "cobalamins". These chemical compounds have a similar molecular structure, each of which shows vitamin activity in a vitamin-deficient biological system. They are referred to as vitamers having vitamin activity as a coenzyme, meaning that its presence is required for some enzyme-catalyzed reactions.[16][17] adenosylcobalamin cyanocobalamin, the adenosyl ligand in vitamin B12 is replaced by cyanide. hydroxocobalamin, the adenosyl ligand in vitamin B12 is replaced by hydroxide. methylcobalamin, the adenosyl ligand in vitamin B12 is replaced by methyl. Cyanocobalamin is a manufactured form of B12. Bacterial fermentation creates AdoB12 and MeB12, which are converted to cyanocobalamin by the addition of potassium cyanide in the presence of sodium nitrite and heat. Once consumed, cyanocobalamin is converted to the biologically active AdoB12 and MeB12. The two bioactive forms of vitamin B12 are methylcobalamin in cytosol and adenosylcobalamin in mitochondria.[18] Cyanocobalamin is the most common form used in dietary supplements and food fortification because cyanide stabilizes the molecule against degradation. Methylcobalamin is also offered as a dietary supplement.[16] There is no advantage to the use of adenosylcobalamin or methylcobalamin forms for the treatment of vitamin B12 deficiency.[19][4] Hydroxocobalamin can be injected intramuscularly to treat vitamin B12 deficiency.[20] It can also be injected intravenously for the purpose of treating cyanide poisoning, as the hydroxyl group is displaced by cyanide, creating a non-toxic cyanocobalamin that is excreted in urine.[21] Pseudovitamin B12 refers to compounds that are corrinoids with a structure similar to the vitamin, but without vitamin activity.[22][18] Pseudovitamin B12 is the majority corrinoid in spirulina, an algal dietary supplement sometimes erroneously claimed as having this vitamin activity.[23] Antivitamin B12 compounds (often synthetic B12 analogues) not only have no vitamin action, but also actively interfere with the activity of true vitamin B12. The design of these compounds mainly involves the replacement of the metal ion with rhodium, nickel, or zinc, or may have an inactive ligand attached, such as 4-ethylphenyl. These compounds have the potential for use in analyzing B12 pathways or even attacking B12-dependent pathogens.[24] Main article: Vitamin B12 deficiency Vitamin B12 deficiency can potentially cause severe and irreversible damage, especially to the brain and nervous system.[6][25] Deficiency at levels only slightly lower than normal can cause a range of symptoms such as fatigue, feeling weak, lightheadedness, dizziness, breathlessness, headaches, mouth ulcers, upset stomach, decreased appetite, difficulty walking (staggering balance problems),[13][26] muscle weakness, depression, poor memory, poor reflexes, confusion, pale skin and feeling abnormal sensations, especially in people over age 60.[6][13][27] Vitamin B12 deficiency can also cause symptoms of mania and psychosis.[28][29] Among other problems, weakened immunity, reduced fertility and interruption of blood circulation in women may occur.[30] The main type of vitamin B12 deficiency anemia is pernicious anemia,[31] characterized by a triad of symptoms: Anemia with bone marrow promegaloblastosis (megaloblastic anemia).[32] This is due to the inhibition of DNA synthesis (specifically purines and thymidine).[medical citation needed] Gastrointestinal symptoms: alteration in bowel motility, such as mild diarrhea or constipation, and loss of bladder or bowel control.[33] These are thought to be due to defective DNA synthesis inhibiting replication in tissue sites with a high turnover of cells. This may also be due to the autoimmune attack on the parietal cells of the stomach in pernicious anemia. There is an association with gastric antral vascular ectasia (which can be referred to as watermelon stomach), and pernicious anemia.[34] Neurological symptoms: sensory or motor deficiencies (absent reflexes, diminished vibration or soft touch sensation) and subacute combined degeneration of the spinal cord.[32][35] Deficiency symptoms in children include developmental delay, regression, irritability, involuntary movements and hypotonia.[36] Vitamin B12 deficiency is most commonly caused by malabsorption, but can also result from low intake, immune gastritis, low presence of binding proteins, or use of certain medications.[6] Vegans—people who choose to not consume any animal-sourced foods—are at risk because plant-sourced foods do not contain the vitamin in sufficient amounts to prevent vitamin deficiency.[37] Vegetarians—people who consume animal byproducts such as dairy products and eggs, but not the flesh of any animal—are also at risk. Vitamin B12 deficiency has been observed in between 40% and 80% of the vegetarian population who do not also take a vitamin B12 supplement or consume vitamin-fortified food.[38] In Hong Kong and India, vitamin B12 deficiency has been found in roughly 80% of the vegan population. As with vegetarians, vegans can avoid this by consuming a dietary supplement or eating B12 fortified food such as cereal, plant-based milks, and nutritional yeast as a regular part of their diet.[39] The elderly are at increased risk because they tend to produce less stomach acid as they age, a condition known as achlorhydria, thereby increasing their probability of B12 deficiency due to reduced absorption.[2] Nitrous oxide overdose or overuse converts the active monovalent form of vitamin B12 to the inactive bivalent form.[40] The U.S. Recommended Dietary Allowance (RDA) for pregnancy is 2.6 micrograms per day (μg/d), for lactation 2.8 μg/d. Determination of these values was based on an RDA of 2.4 μg/d for non-pregnant women, plus what will be transferred to the fetus during pregnancy and what will be delivered in breast milk.[16][41]:972 However, looking at the same scientific evidence, the European Food Safety Authority (EFSA) sets adequate intake (AI) at 4.5 μg/d for pregnancy and 5.0 μg/d for lactation.[42] Low maternal vitamin B12, defined as serum concentration less than 148 pmol/L, increases the risk of miscarriage, preterm birth and newborn low birth weight.[43][41] During pregnancy the placenta concentrates B12, so that newborn infants have a higher serum concentration than their mothers.[16] As it is recently absorbed vitamin content that more effectively reaches the placenta, the vitamin consumed by the mother-to-be is more important than that contained in her liver tissue.[16][44] Women who consume little animal-sourced food, or who are vegetarian or vegan, are at higher risk of becoming vitamin depleted during pregnancy than those who consume more animal products. This depletion can lead to anemia, and also an increased risk that their breastfed infants become vitamin deficient.[44][41] Vitamin B12 is not one of the supplements recommended by the World Health Organization for healthy women who are pregnant,[14] however, vitamin B12 is often suggested during pregnancy in a multivitamin along with folic acid[45][46] especially for pregnant mothers who follow a vegetarian or vegan diet.[47] Low vitamin concentrations in human milk occur in families with low socioeconomic status or low consumption of animal products.[41]:971,973 Only a few countries, primarily in Africa, have mandatory food fortification programs for either wheat flour or maize flour; India has a voluntary fortification program.[48] What the nursing mother consumes is more important than her liver tissue content, as it is recently absorbed vitamin that more effectively reaches breast milk.[41]:973 Breast milk B12 decreases over months of nursing in both well-nourished and vitamin-deficient mothers.[41]:973–974 Exclusive or near-exclusive breastfeeding beyond six months is a strong indicator of low serum vitamin status in nursing infants. This is especially true when the vitamin status is poor during the pregnancy and if the early-introduced foods fed to the still-breastfeeding infant are vegan.[41]:974–975 The risk of deficiency persists if the post-weaning diet is low in animal products.[41]:974–975 Signs of low vitamin levels in infants and young children can include anemia, poor physical growth, and neurodevelopmental delays.[41]:975 Children diagnosed with low serum B12 can be treated with intramuscular injections, then transitioned to an oral dietary supplement.[41]:976 Various methods of gastric bypass or gastric restriction surgery are used to treat morbid obesity. Roux-en-Y gastric bypass surgery (RYGB) but not sleeve gastric bypass surgery or gastric banding, increases the risk of vitamin B12 deficiency and requires preventive post-operative treatment with either injected or high-dose oral supplementation.[49][50][51] For post-operative oral supplementation, 1000 μg/d may be needed to prevent vitamin deficiency.[51] According to one review: "At present, no 'gold standard' test exists for the diagnosis of vitamin B12 deficiency and as a consequence the diagnosis requires consideration of both the clinical state of the patient and the results of investigations."[52] The vitamin deficiency is typically suspected when a routine complete blood count shows anemia with an elevated mean corpuscular volume (MCV). In addition, on the peripheral blood smear, macrocytes and hypersegmented polymorphonuclear leukocytes may be seen. Diagnosis is supported based on vitamin B12 blood levels below 150–180 pmol/L (200–250 pg/mL) in adults.[53] However, serum values can be maintained while tissue B12 stores are becoming depleted. Therefore, serum B12 values above the cut-off point of deficiency do not necessarily confirm adequate B12 status.[2] For this reason, elevated serum homocysteine over 15 micromol/L and methylmalonic acid (MMA) over 0.271 micromol/L are considered better indicators of B12 deficiency, rather than relying only on the concentration of B12 in blood.[2] However, elevated MMA is not conclusive, as it is seen in people with B12 deficiency, but also in elderly people who have renal insufficiency,[29] and elevated homocysteine is not conclusive, as it is also seen in people with folate deficiency.[54] In addition, elevated methylmalonic acid levels may also be related to metabolic disorders such as methylmalonic acidemia.[55] If nervous system damage is present and blood testing is inconclusive, a lumbar puncture may be carried out to measure cerebrospinal fluid B12 levels.[56] Serum haptocorrin binds 80-90% of circulating B12, rendering it unavailable for cellular delivery by transcobalamin II. This is conjectured to be a circulating storage function.[57] Several serious, even life-threatening diseases cause elevated serum haptocorrin, measured as abnormally high serum vitamin B12, while at the same time potentially manifesting as a symptomatic vitamin deficiency because of insufficient vitamin bound to transcobalamin II which transfers the vitamin to cells.[58] A vitamin B12 solution (hydroxocobalamin) in a multi-dose bottle, with a single dose drawn up into a syringe for injection. Preparations are usually bright red. Severe vitamin B12 deficiency is initially corrected with daily intramuscular injections of 1000 μg of the vitamin, followed by maintenance via monthly injections of the same amount or daily oral dosing of 1000 μg. The oral daily dose far exceeds the vitamin requirement because the normal transporter protein-mediated absorption is absent, leaving only very inefficient intestinal passive absorption.[59][60] Injection side effects include skin rash, itching, chills, fever, hot flushes, nausea and dizziness. Oral maintenance treatment avoids this problem and significantly reduces the cost of treatment.[59][60] For cyanide poisoning, a large amount of hydroxocobalamin may be given intravenously and sometimes in combination with sodium thiosulfate.[61][62] The mechanism of action is straightforward: the hydroxycobalamin hydroxide ligand is displaced by the toxic cyanide ion, and the resulting non-toxic cyanocobalamin is excreted in urine.[63] Some research shows that most people in the United States and the United Kingdom consume sufficient vitamin B12.[2][10] However, other research suggests that the proportion of people with low or marginal levels of vitamin B12 is up to 40% in the Western world.[2] Grain-based foods can be fortified by having the vitamin added to them. Vitamin B12 supplements are available as single or multivitamin tablets. Pharmaceutical preparations of vitamin B12 may be given by intramuscular injection.[6][64] Since there are few non-animal sources of the vitamin, vegans are advised to consume a dietary supplement or fortified foods for B12 intake, or risk serious health consequences.[6] Children in some regions of developing countries are at particular risk due to increased requirements during growth coupled with diets low in animal-sourced foods. The US National Academy of Medicine updated estimated average requirements (EARs) and recommended dietary allowances (RDAs) for vitamin B12 in 1998.[6] The EAR for vitamin B12 for women and men ages 14 and up is 2.0 μg/day; the RDA is 2.4 μg/d. RDA is higher than EAR to identify amounts that will cover people with higher-than-average requirements. RDA for pregnancy equals 2.6 μg/day. RDA for lactation equals 2.8 μg/d. For infants up to 12 months, the adequate intake (AI) is 0.4–0.5 μg/day. (AIs are established when there is insufficient information to determine EARs and RDAs.) For children ages 1–13 years, the RDA increases with age from 0.9 to 1.8 μg/day. Because 10 to 30 percent of older people may be unable to effectively absorb vitamin B12 naturally occurring in foods, those older than 50 years should meet their RDA mainly by consuming foods fortified with vitamin B12 or a supplement containing vitamin B12. As for safety, tolerable upper intake levels (known as ULs) are set for vitamins and minerals when evidence is sufficient. In the case of vitamin B12 there is no UL, as there is no human data for adverse effects from high doses. Collectively the EARs, RDAs, AIs, and ULs are referred to as dietary reference intakes (DRIs).[16] The European Food Safety Authority (EFSA) refers to the collective set of information as "dietary reference values", with population reference intake (PRI) instead of RDA, and average requirement instead of EAR. AI and UL are defined by EFSA the same as in the United States. For women and men over age 18, the adequate intake (AI) is set at 4.0 μg/day. AI for pregnancy is 4.5 μg/day, and for lactation 5.0 μg/day. For children aged 1–14 years, the AIs increase with age from 1.5 to 3.5 μg/day. These AIs are higher than the U.S. RDAs.[42] The EFSA also reviewed the safety question and reached the same conclusion as in the United States—that there was not sufficient evidence to set a UL for vitamin B12.[65] The Japan National Institute of Health and Nutrition set the RDA for people ages 12 and older at 2.4 μg/day.[66] The World Health Organization also uses 2.4 μg/day as the adult recommended nutrient intake for this vitamin.[67] For U.S. food and dietary supplement labeling purposes, the amount in a serving is expressed as a "percent of daily value" (%DV). For vitamin B12 labeling purposes, 100% of the daily value was 6.0 μg, but on 27 May 2016, it was revised downward to 2.4 μg (see Reference Daily Intake).[68][69] Compliance with the updated labeling regulations was required by 1 January 2020 for manufacturers with US$10 million or more in annual food sales, and by 1 January 2021 for manufacturers with lower volume food sales.[70][71] Vitamin B12 is produced in nature by certain bacteria, and archaea.[72][73][74] It is synthesized by some bacteria in the gut microbiota in humans and other animals, but it has long been thought that humans cannot absorb this as it is made in the colon, downstream from the small intestine, where the absorption of most nutrients occurs.[75] Ruminants, such as cows and sheep, are foregut fermenters, meaning that plant food undergoes microbial fermentation in the rumen before entering the true stomach (abomasum), and thus they are absorbing vitamin B12 produced by bacteria.[75][76] Other mammalian species (examples: rabbits, pikas, beaver, guinea pigs) consume high-fiber plants which pass through the gastrointestinal tract and undergo bacterial fermentation in the cecum and large intestine. In this hindgut fermentation, the material from the cecum is expelled as "cecotropes" and are re-ingested, a practice referred to as cecotrophy. Re-ingestion allows for absorption of nutrients made available by bacterial fermentation, and also of vitamins and other nutrients synthesized by the gut bacteria, including vitamin B12.[76] Non-ruminant, non-hindgut herbivores may have an enlarged forestomach and/or small intestine to provide a place for bacterial fermentation and B-vitamin production, including B12.[76] For gut bacteria to produce vitamin B12, the animal must consume sufficient amounts of cobalt.[77] Soil that is deficient in cobalt may result in B12 deficiency, and B12 injections or cobalt supplementation may be required for livestock.[78] Animals store vitamin B12 from their diets in their livers and muscles and some pass the vitamin into their eggs and milk. Meat, liver, eggs, and milk are therefore sources of the vitamin for other animals, including humans.[64][2][79] For humans, the bioavailability from eggs is less than 9%, compared to 40% to 60% from fish, fowl, and meat.[80] Insects are a source of B12 for animals (including other insects and humans).[79][81] Animal-derived food sources with a high concentration of vitamin B12 include liver and other organ meats from lamb, veal, beef, and turkey; also shellfish and crab meat.[6][64][82] There is some evidence that bacterial fermentation of plant foods and symbiotic relationships between algae and bacteria can provide vitamin B12. However, the Academy of Nutrition and Dietetics considers plant and algae sources "unreliable", stating that vegans should turn to fortified foods and supplements instead.[37] Natural plant and algae sources of vitamin B12 include fermented plant foods such as tempeh[83][84] and seaweed-derived foods such as nori and laverbread.[85][86][87] Methylcobalamin has been identified in Chlorella vulgaris.[88] Since only bacteria and some archea possess the genes and enzymes necessary to synthesize vitamin B12, plant and algae sources all obtain the vitamin secondarily from symbiosis with various species of bacteria,[5] or in the case of fermented plant foods, from bacterial fermentation.[83] Foods for which vitamin B12-fortified versions are available include breakfast cereals, plant-derived milk substitutes such as soy milk and oat milk, energy bars, and nutritional yeast.[82] The fortification ingredient is cyanocobalamin. Microbial fermentation yields adenosylcobalamin, which is then converted to cyanocobalamin by the addition of potassium cyanide or thiocyanate in the presence of sodium nitrite and heat.[89] As of 2019, nineteen countries require food fortification of wheat flour, maize flour, or rice with vitamin B12. Most of these are in southeast Africa or Central America.[48] Vegan advocacy organizations, among others, recommend that every vegan consume B12 from either fortified foods or supplements.[6][39][90][91] A blister pack of 500 μg methylcobalamin tablets Vitamin B12 is included in multivitamin pills; in some countries grain-based foods, such as bread and pasta, are fortified with B12.[2] In the US, non-prescription products can be purchased providing up to 1,000 μg each, and it is a common ingredient in energy drinks and energy shots, usually at many times the recommended dietary allowance of B12.[2] The vitamin can also be supplied on prescription and delivered via injection or other means.[2] When used in supplementation, all of the vitamin B12 vitamers have been argued to be beneficial, with there not being clear evidence that any are relatively more or less effective.[92][93][94] The amount of cyanide in cyanocobalamin is generally not considered a health risk, since even in a 1,000 μg dose, the 20 μg of cyanide it contains is less than the daily consumption of cyanide from food.[92] Injection of hydroxycobalamin is often used if digestive absorption is impaired,[2] but this course of action may not be necessary with high-dose oral supplements (such as 0.5–1.0 mg or more),[95][96] because with large quantities of the vitamin taken orally, even the 1% to 5% of free crystalline B12 that is absorbed along the entire intestine by passive diffusion may be sufficient to provide a necessary amount.[97] A person with cobalamin C disease, a rare autosomal, recessive, inheritance disease which results in combined methylmalonic aciduria and homocystinuria),[98] can be treated with intravenous or intramuscular hydroxocobalamin.[99] Conventional administration does not ensure specific distribution and controlled release of vitamin B12. Moreover, therapeutic protocols involving injection require health care people and commuting of patients to the hospital thus increasing the cost of the treatment and impairing the lifestyle of patients. Targeted delivery of vitamin B12 is a major focus of modern prescriptions. For example, conveying the vitamin to the bone marrow and nerve cells would help myelin recovery. Currently, several nanocarriers strategies are being developed for improving vitamin B12 delivery to simplify administration, reduce costs, improve pharmacokinetics, and ameliorate the quality of patients' lives.[100] Gastric acid is needed to release vitamin B12 from protein for absorption. Reduced secretion of gastric acid and pepsin, from the use of H2 blocker or proton-pump inhibitor (PPI) drugs, can reduce the absorption of protein-bound (dietary) vitamin B12, although not of supplemental vitamin B12. H2-receptor antagonist examples include cimetidine, famotidine, nizatidine, and ranitidine. PPIs examples include omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. Clinically significant vitamin B12 deficiency and megaloblastic anemia are unlikely, unless these drug therapies are prolonged for two or more years, or if in addition, the person's dietary intake is below recommended levels. Symptomatic vitamin deficiency is more likely if the person is rendered achlorhydric (a complete absence of gastric acid secretion), which occurs more frequently with proton pump inhibitors than H2 blockers.[101] Reduced serum levels of vitamin B12 occur in up to 30% of people taking long-term anti-diabetic metformin.[102][103] Deficiency does not develop if dietary intake of vitamin B12 is adequate or prophylactic B12 supplementation is given. If the deficiency is detected, metformin can be continued while the deficiency is corrected with B12 supplements.[104] Certain medications can decrease the absorption of orally consumed vitamin B12, including colchicine, extended-release potassium products, and antibiotics such as gentamicin, neomycin and tobramycin.[105] Anti-seizure medications phenobarbital, pregabalin, primidone and topiramate are associated with lower than normal serum vitamin concentration. However, serum levels were higher in people prescribed valproate.[106] In addition, certain drugs may interfere with laboratory tests for the vitamin, such as amoxicillin, erythromycin, methotrexate and pyrimethamine.[105] Methylcobalamin (shown) is a form of vitamin B12. Physically it resembles the other forms of vitamin B12, occurring as dark red crystals that freely form cherry-colored transparent solutions in water. Vitamin B12 is the most chemically complex of all the vitamins.[6] The structure of B12 is based on a corrin ring, which is similar to the porphyrin ring found in heme. The central metal ion is cobalt. As isolated as an air-stable solid and available commercially, cobalt in vitamin B12 (cyanocobalamin and other vitamers) is present in its +3 oxidation state. Biochemically, the cobalt center can take part in both two-electron and one-electron reductive processes to access the "reduced" (B12r, +2 oxidation state) and "super-reduced" (B12s, +1 oxidation state) forms. The ability to shuttle between the +1, +2, and +3 oxidation states is responsible for the versatile chemistry of vitamin B12, allowing it to serve as a donor of deoxyadenosyl radical (radical alkyl source) and as a methyl cation equivalent (electrophilic alkyl source).[107] The structures of the four most common vitamers of cobalamin, together with some synonyms. The structure of the 5'-deoxyadenosyl group, which forms the R group of adenosylcobalamin is also shown. Four of the six coordination sites are provided by the corrin ring and a fifth by a dimethylbenzimidazole group. The sixth coordination site, the reactive center, is variable, being a cyano group (–CN), a hydroxyl group (–OH), a methyl group (–CH_3) or a 5′-deoxyadenosyl group. Historically, the covalent carbon–cobalt bond is one of the first examples of carbon-metal bonds to be discovered in biology. The hydrogenases and, by necessity, enzymes associated with cobalt utilization, involve metal-carbon bonds.[108] Animals can convert cyanocobalamin and hydroxocobalamin to the bioactive forms adenosylcobalamin and methylcobalamin by enzymatically replacing the cyano or hydroxyl groups. Several methods have been used to determine the vitamin B12 content in foods including microbiological assays, chemiluminescence assays, polarographic, spectrophotometric, and high-performance liquid chromatography processes.[109] The microbiological assay has been the most commonly used assay technique for foods, utilizing certain vitamin B12-requiring microorganisms, such as Lactobacillus delbrueckii subsp. lactis ATCC7830.[80] However, it is no longer the reference method due to the high measurement uncertainty of vitamin B12.[110] Furthermore, this assay requires overnight incubation and may give false results if any inactive vitamin B12 analogues are present in the foods.[111] Currently, radioisotope dilution assay (RIDA) with labeled vitamin B12 and hog IF (pigs) have been used to determine vitamin B12 content in food.[80] Previous reports have suggested that the RIDA method can detect higher concentrations of vitamin B12 in foods compared to the microbiological assay method.[80][109] Vitamin B12 functions as a coenzyme, meaning that its presence is required in some enzyme-catalyzed reactions.[16][17] Listed here are the three classes of enzymes that sometimes require B12 to function (in animals): Isomerases Rearrangements in which a hydrogen atom is directly transferred between two adjacent atoms with concomitant exchange of the second substituent, X, which may be a carbon atom with substituents, an oxygen atom of an alcohol, or an amine. These use the AdoB12 (adenosylcobalamin) form of the vitamin.[112] Methyltransferases Methyl (–CH_3) group transfers between two molecules. These use the MeB12 (methylcobalamin) form of the vitamin.[113] Dehalogenases Some species of anaerobic bacteria synthesize B12-dependent dehalogenases, which have potential commercial applications for degrading chlorinated pollutants. The microorganisms may either be capable of de novo corrinoid biosynthesis or are dependent on exogenous vitamin B12.[114][115] In humans, two major coenzyme B12-dependent enzyme families corresponding to the first two reaction types, are known. These are typified by the following two enzymes: Simplified schematic diagram of the propionate metabolic pathway. Methylmalonyl-CoA mutase requires the coenzyme adenosylcobalamin to convert L-methylmalonyl-CoA into succinyl-CoA. Otherwise, methylmalonic acid accumulates, making it a marker for vitamin B12 deficiency, among other things. Methylmalonyl coenzyme A mutase (MUT) is an isomerase enzyme that uses the AdoB12 form and reaction type 1 to convert L-methylmalonyl-CoA to succinyl-CoA, an important step in the catabolic breakdown of some amino acids into succinyl-CoA, which then enters energy production via the citric acid cycle.[112] This functionality is lost in vitamin B12 deficiency, and can be measured clinically as an increased serum methylmalonic acid (MMA) concentration. The MUT function is necessary for proper myelin synthesis.[4] Based on animal research, it is thought that the increased methylmalonyl-CoA hydrolyzes to form methylmalonate (methylmalonic acid), a neurotoxic dicarboxylic acid, causing neurological deterioration.[116] Simplified schematic diagram of the folate methionine cycle. Methionine synthase transfers the methyl group to the vitamin and then transfers the methyl group to homocysteine, converting that to methionine. Methionine synthase, coded by MTR gene, is a methyltransferase enzyme which uses the MeB12 and reaction type 2 to transfer a methyl group from 5-methyltetrahydrofolate to homocysteine, thereby generating tetrahydrofolate (THF) and methionine.[113] This functionality is lost in vitamin B12 deficiency, resulting in an increased homocysteine level and the trapping of folate as 5-methyl-tetrahydrofolate, from which THF (the active form of folate) cannot be recovered. THF plays an important role in DNA synthesis, so reduced availability of THF results in ineffective production of cells with rapid turnover, in particular red blood cells, and also intestinal wall cells which are responsible for absorption. THF may be regenerated via MTR or may be obtained from fresh folate in the diet. Thus all of the DNA synthetic effects of B12 deficiency, including the megaloblastic anemia of pernicious anemia, resolve if sufficient dietary folate is present. Thus the best-known "function" of B12 (that which is involved with DNA synthesis, cell division, and anemia) is a facultative function that is mediated by B12-conservation of an active form of folate which is needed for efficient DNA production.[113] Other cobalamin-requiring methyltransferase enzymes are also known in bacteria, such as Me-H4-MPT, coenzyme M methyltransferase.[117] Vitamin B12 is absorbed by a B12-specific transport proteins or via passive diffusion.[16] Transport-mediated absorption and tissue delivery is a complex process involving three transport proteins: haptocorrin (HC), intrinsic factor (IF) and transcobalamin II (TC2), and respective membrane receptor proteins. HC is present in saliva. As vitamin-containing food is digested by hydrochloric acid and pepsin secreted into the stomach, HC binds the vitamin and protects it from acidic degradation.[16][118] Upon leaving the stomach the hydrochloric acid of the chyme is neutralized in the duodenum by bicarbonate,[119] and pancreatic proteases release the vitamin from HC, making it available to be bound by IF, which is a protein secreted by gastric parietal cells in response to the presence of food in the stomach. IF delivers the vitamin to receptor proteins cubilin and amnionless, which together form the cubam receptor in the distal ileum. The receptor is specific to the IF-B12 complex, and so will not bind to any vitamin content that is not bound to IF.[16][118] Investigations into the intestinal absorption of B12 confirm that the upper limit of absorption per single oral dose is about 1.5 μg, with 50% efficiency. In contrast, the passive diffusion process of B12 absorption — normally a very small portion of total absorption of the vitamin from food consumption — may exceed the haptocorrin- and IF-mediated absorption when oral doses of B12 are very large, with roughly 1% efficiency. Thus, dietary supplement B12 supplementation at 500 to 1000 μg per day allows pernicious anemia and certain other defects in B12 absorption to be treated with daily oral megadoses of B12 without any correction of the underlying absorption defects.[118] After the IF/B12 complex binds to cubam the complex is disassociated and the free vitamin is transported into the portal circulation. The vitamin is then transferred to TC2, which serves as the circulating plasma transporter, hereditary defects in the production of TC2 and its receptor may produce functional deficiencies in B12 and infantile megaloblastic anemia, and abnormal B12 related biochemistry, even in some cases with normal blood B12 levels. For the vitamin to serve inside cells, the TC2-B12 complex must bind to a cell receptor protein and be endocytosed. TC2 is degraded within a lysosome, and free B12 is released into the cytoplasm, where it is transformed into the bioactive coenzyme by cellular enzymes.[118][120] Antacid drugs that neutralize stomach acid, as well as acid-suppressing agents such as proton-pump inhibitors, can inhibit the absorption of vitamin B12 by preventing its release from food in the stomach.[121] Other causes of B12 malabsorption include intrinsic factor deficiency, pernicious anemia, bariatric surgery, pancreatic insufficiency, obstructive jaundice, tropical sprue, celiac disease, and radiation enteritis affecting the distal ileum.[118] Age is also a contributing factor: elderly individuals are often achlorhydric due to reduced parietal cell function in the stomach, increasing their risk of vitamin B12 deficiency.[122] The ability to absorb vitamin B12 declines with age, particularly in individuals over 60.[123] How fast B12 levels change depends on the balance between how much B12 is obtained from the diet, how much is secreted and how much is absorbed. The total amount of vitamin B12 stored in the body is about 2–5 mg in adults. Around 50% of this is stored in the liver. Approximately 0.1% of this is lost per day by secretions into the gut, as not all these secretions are reabsorbed. Bile is the main form of B12 excretion; most of the B12 secreted in the bile is recycled via enterohepatic circulation. Excess B12 beyond the blood's binding capacity is typically excreted in urine. Owing to the extremely efficient enterohepatic circulation of B12, the liver can store 3 to 5 years' worth of vitamin B12; therefore, nutritional deficiency of this vitamin is rare in adults in the absence of malabsorption disorders.[16] In the absence of intrinsic factor or distal ileum receptors, only months to a year of vitamin B12 are stored.[124] Vitamin B12 through its involvement in one-carbon metabolism plays a key role in cellular reprogramming and tissue regeneration and epigenetic regulation. Cellular reprogramming is the process by which somatic cells can be converted to a pluripotent state. Vitamin B12 levels affect the histone modification H3K36me3, which suppresses illegitimate transcription outside of gene promoters. Mice undergoing in vivo reprogramming were found to become depleted in B12 and show signs of methionine starvation while supplementing reprogramming mice and cells with B12 increased reprogramming efficiency, indicating a cell-intrinsic effect.[125][126] Main article: Cobalamin biosynthesis Vitamin B12 is derived from a tetrapyrrolic structural framework created by the enzymes deaminase and cosynthetase which transform aminolevulinic acid via porphobilinogen and hydroxymethylbilane to uroporphyrinogen III. The latter is the first macrocyclic intermediate common to heme, chlorophyll, siroheme and B12 itself.[127][128] Later steps, especially the incorporation of the additional methyl groups of its structure, were investigated using 13C methyl-labelled S-adenosyl methionine. It was not until a genetically engineered strain of Pseudomonas denitrificans was used, in which eight of the genes involved in the biosynthesis of the vitamin had been overexpressed, that the complete sequence of methylation and other steps could be determined, thus fully establishing all the intermediates in the pathway.[129][130] Species from the following genera and the following individual species are known to synthesize B12: Propionibacterium shermanii, Pseudomonas denitrificans, Streptomyces griseus, Acetobacterium, Aerobacter, Agrobacterium, Alcaligenes, Azotobacter, Bacillus, Clostridium, Corynebacterium, Flavobacterium, Lactobacillus, Micromonospora, Mycobacterium, Nocardia, Proteus, Rhizobium, Salmonella, Serratia, Streptococcus and Xanthomonas.[131][132] Industrial production of B12 is achieved through fermentation of selected microorganisms.[133] Streptomyces griseus, a bacterium once thought to be a fungus, was the commercial source of vitamin B12 for many years.[134] The species Pseudomonas denitrificans and Propionibacterium freudenreichii subsp. shermanii are more commonly used today.[133] These are grown under special conditions to enhance yield. Rhone-Poulenc improved yield via genetic engineering P. denitrificans.[135] Propionibacterium, the other commonly used bacteria, produce no exotoxins or endotoxins and are generally recognized as safe (have been granted GRAS status) by the Food and Drug Administration of the United States.[136] The total world production of vitamin B12 in 2008 was 35,000 kg (77,000 lb).[137] Main article: Vitamin B12 total synthesis The complete laboratory synthesis of B12 was achieved by Robert Burns Woodward[138] and Albert Eschenmoser in 1972.[139][140] The work required the effort of 91 postdoctoral fellows (mostly at Harvard) and 12 PhD students (at ETH Zurich) from 19 nations. The synthesis constitutes a formal total synthesis, since the research groups only prepared the known intermediate cobyric acid, whose chemical conversion to vitamin B12 was previously reported. This synthesis of vitamin B12 is of no practical consequence due to its length, taking 72 chemical steps and giving an overall chemical yield well under 0.01%.[141] Although there have been sporadic synthetic efforts since 1972,[140] the Eschenmoser–Woodward synthesis remains the only completed (formal) total synthesis. Further information: Vitamin § History Between 1849 and 1887, Thomas Addison described a case of pernicious anemia, William Osler and William Gardner first described a case of neuropathy, Hayem described large red cells in the peripheral blood in this condition, which he called "giant blood corpuscles" (now called macrocytes), Paul Ehrlich identified megaloblasts in the bone marrow, and Ludwig Lichtheim described a case of myelopathy.[142] During the 1920s, George Whipple discovered that ingesting large amounts of raw liver seemed to most rapidly cure the anemia of blood loss in dogs, and hypothesized that eating liver might treat pernicious anemia.[143] Edwin Cohn prepared a liver extract that was 50 to 100 times more potent in treating pernicious anemia than the natural liver products. William Castle demonstrated that gastric juice contained an "intrinsic factor" which when combined with meat ingestion resulted in absorption of the vitamin in this condition.[142] In 1934, George Whipple shared the 1934 Nobel Prize in Physiology or Medicine with William P. Murphy and George Minot for discovery of an effective treatment for pernicious anemia using liver concentrate, later found to contain a large amount of vitamin B12.[142][144] While working at the Bureau of Dairy Industry, U.S. Department of Agriculture, Mary Shaw Shorb was assigned work on the bacterial strain Lactobacillus lactis Dorner (LLD), which was used to make yogurt and other cultured dairy products. The culture medium for LLD required liver extract. Shorb knew that the same liver extract was used to treat pernicious anemia (her father-in-law had died from the disease), and concluded that LLD could be developed as an assay method to identify the active compound. While at the University of Maryland, she received a small grant from Merck, and in collaboration with Karl Folkers from that company, developed the LLD assay. This identified "LLD factor" as essential for the bacteria's growth.[145] Shorb, Folker and Alexander R. Todd, at the University of Cambridge, used the LLD assay to extract the anti-pernicious anemia factor from liver extracts, purify it, and name it vitamin B12.[146] In 1955, Todd helped elucidate the structure of the vitamin. The complete chemical structure of the molecule was determined by Dorothy Hodgkin based on crystallographic data and published in 1955[147] and 1956,[148] for which, and for other crystallographic analyses, she was awarded the Nobel Prize in Chemistry in 1964.[149] Hodgkin went on to decipher the structure of insulin.[149] George Whipple, George Minot and William Murphy were awarded the Nobel Prize in 1934 for their work on the vitamin. Three other Nobel laureates, Alexander R. Todd (1957), Dorothy Hodgkin (1964) and Robert Burns Woodward (1965) made important contributions to its study.[150] Nobel laureates for discoveries relating to vitamin B12 George Whipple George Minot William P. Murphy Alexander R. Todd Dorothy Hodgkin Robert Burns Woodward Industrial production of vitamin B12 is achieved through fermentation of selected microorganisms.[133] As noted above, the completely synthetic laboratory synthesis of B12 was achieved by Robert Burns Woodward and Albert Eschenmoser in 1972, though this process has no commercial potential, requiring more than 70 steps and having a yield well below 0.01%.[141] In the 1970s, John A. Myers, a physician residing in Baltimore, developed a program of injecting vitamins and minerals intravenously for various medical conditions. The formula included 1000 μg of cyanocobalamin. This came to be known as the Myers' cocktail. After he died in 1984, other physicians and naturopaths took up prescribing "intravenous micronutrient therapy" with unsubstantiated health claims for treating fatigue, low energy, stress, anxiety, migraine, depression, immunocompromised, promoting weight loss, and more.[151] However, other than a report on case studies[151] there are no benefits confirmed in the scientific literature.[152] Healthcare practitioners at clinics and spas prescribe versions of these intravenous combination products, but also intramuscular injections of just vitamin B12. A Mayo Clinic review concluded that there is no solid evidence that vitamin B12 injections provide an energy boost or aid weight loss.[153] There is evidence that for elderly people, physicians often repeatedly prescribe and administer cyanocobalamin injections inappropriately, evidenced by the majority of subjects in one large study either having had normal serum concentrations or having not been tested before the injections.[154] Adenosylcobalamin Cobalamin biosynthesis Cyanocobalamin Hydroxocobalamin Methylcobalamin Vitamins Gherasim C, Lofgren M, Banerjee R (May 2013). "Navigating the B(12) road: assimilation, delivery, and disorders of cobalamin". J. Biol. Chem. 288 (19): 13186–13193. doi:10.1074/jbc.R113.458810. PMC 3650358. PMID 23539619. ^ Prieto T, Neuburger M, Spingler B, Zelder F (2016). "Inorganic Cyanide as Protecting Group in the Stereospecific Reconstitution of Vitamin B12 from an Artificial Green Secocorrinoid" (PDF). Org. 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Cyanocobalamin at the U.S. National Library of Medicine Medical Subject Headings (MeSH) Portal: Medicine Retrieved from " La vitamina B12 es una de las más importantes para el cuerpo y forma parte del grupo de vitaminas hidrosolubles, es decir, que se disuelve en agua. Esta sustancia es vital para que el cuerpo pueda metabolizar las proteínas, produzca glóbulos rojos en la sangre y mantenga el sistema nervioso central funcionando correctamente.Esta vitamina se obtiene en gran parte a través de la alimentación y su deficiencia resulta muy extraña, ya que el cuerpo puede almacenar vitamina B12 en el hígado durante muchos años. Sin embargo, una concentración excesiva de esta vitamina en sangre puede afectar la salud considerablemente. ¿Cuáles son las causas de la vitamina B12 alta? Descubre eso y más en este artículo de eSalud.ÍndiceComo mencionamos anteriormente, el hígado es el órgano responsable del almacenamiento de vitamina B12 en el cuerpo, por lo tanto, cualquier desorden en su funcionamiento puede afectar los niveles de esta sustancia en el organismo. Una de las causas más comunes de la vitamina B12 alta son la cirrosis hepática y la hepatitis. Asimismo, el consumo excesivo de bebidas alcohólicas también puede incrementar la concentración de esta sustancia en sangre.Cuando una persona presenta algún tipo de enfermedad hepática, el hígado reacciona liberando la vitamina B12 almacenada, lo cual provoca que haya mayor cantidad de esta vitamina en sangre. No obstante, cuando el hígado está muy afectado por condiciones como la cirrosis, su funcionamiento empieza a ser cada vez más deficiente, lo cual le impide eliminar la vitamina B12 y en lugar de desecharla a través de la orina, el cuero comienza a acumularla.Problemas renalesLa vitamina B12 es liberada por el organismo a través de la orina para evitar su acumulación. Los riñones, son los órganos responsables de desechar esta sustancia y todas las toxinas que estén presentes en el organismo, es decir, actúan como el filtro del cuerpo. Sin embargo, cuando los riñones se encuentran enfermos trabajan de forma deficiente no pueden eliminar correctamente la vitamina B12 liberada por el hígado y se produce un exceso de esta sustancia.Son muchas las causas por las que el funcionamiento renal se puede ver comprometido, pero entre las más comunes encontramos la presencia de cálculos en los riñones, la pielonefritis o infección de un riñón, insuficiencia renal, quistes renales o cáncer de riñón.Médula óseaLa médula ósea es el tejido responsable de la producción de las células sanguíneas: glóbulos rojos, glóbulos blancos y plaquetas. El desorden en la producción de estas células puede causar dos condiciones que están asociadas a la vitamina B12 alta y que ameritan ser tratadas a tiempo para preservar la salud. Entre las enfermedades hematológicas relacionadas con un incremento de vitamina B12 en sangre encontramos:Leucemia mieloide crónica: esta condición es un tipo de cáncer que se produce cuando la médula ósea comienza a producir incontrolablemente un tipo de glóbulos blancos conocido como mieloide. Esta enfermedad es causa principalmente por un problema con el cromosoma filadelfia. Cuando una persona tiene leucemia mieloide crónica, además de tener la vitamina B12 alta, presenta plaquetas y leucocitos altos en sangre, bazo inflamado y puntos rojos en la piel conocidos como petequias.Policitemia vera: la vitamina B12 interviene en el proceso de producción de los glóbulos rojos. La policitemia vera es una condición que ocurre cuando la médula produce de forma excesiva glóbulos rojos, causando mareos, hemorragias, hematomas, dolor de cabeza, prurito y dificultad para respirar entre otros síntomas. La policitemia vera es más común en hombres que en mujeres y se asocia con la vitamina B12 alta porque incrementa la proteína que transporta dicha vitamina en el cuerpo.Algunos tipos de cáncer Si bien el cáncer no suele ser la causa más común de tener la vitamina B12 alta en sangre, algunos tipos de esta enfermedad pueden causar este síntoma. Entre los tipos de cáncer asociados al incremento de la vitamina B12 se encuentran el cáncer de mama, de hígado, renal y gastrointestinal. Sin embargo, estas afecciones suelen presentar otra serie de síntomas que resultan determinantes para el diagnóstico.¿Alimentación?¡No! Si bien la vitamina B12 la obtenemos a través de nuestra ingesta alimenticia, es casi imposible que la acumulación de esta sustancia en el organismo esté provocada por una ingesta excesiva de alimenticios ricos en vitamina B12. Por lo tanto, es importante resaltar que esta condición suele presentarse debido a un trastorno en el funcionamiento del cuerpo humano que impide liberar adecuadamente la concentración de vitamina en el cuerpo. También existe la posibilidad de que sea una condición particular del cuerpo de una persona, lo cual puede causar niveles elevados de vitamina B12 sin causa aparente.Síntomas de la vitamina B12 alta Por lo general, cuando una persona tiene la vitamina B12 alta en sangre no suele presentar síntomas importantes, razón por la que resulta tan difícil diagnosticar esta condición. Sin embargo, no todos corren con la misma suerte y hay quienes presentan los siguientes síntomas:Mareos y dolor de cabeza.Dolores musculares.Erupción en la piel.Prurito después de ducharse con agua caliente.Nerviosismo, ansiedad y palpitaciones cardíacas aceleradas.Dolor estomacal y diarrea.Tratamiento para la vitamina B12 alta Si bien lo primordial es descubrir cuál ha sido la causa de este desorden corporal, un exceso de esta sustancia en el organismo suele revertirse una vez que la persona comienza a recibir tratamiento para su causa de origen. Es decir, no resulta necesario modificar hábitos alimenticios o tomar medicamentos, lo esencial es saber por qué la vitamina B12 está alta y poder así atacar el problema de raíz.Evitar el consumo de suplementos vitamínicos o inyecciones de vitamina B12 sin prescripción médica es una forma de evitar el incremento excesivo de esta sustancia en el cuerpo. Una dieta balanceada es suficiente para obtener todos los nutrientes y vitaminas necesarios para estar saludable, por el contrario, el exceso de vitamina B12 y cualquier otra sustancia no te garantiza estar mejor, solo compromete la salud de tu organismo. Por lo tanto, acudir al médico en caso de presentar cualquier síntoma de vitamina b12 alta y evitar la automedicación con suplementos es vital para preservar el bienestar del cuerpo.