Personalized Psychiatry and Neurology

Review

Prospects for studying the pharmacokinetics, pharmacodynamics and pharmacogenetics of vitamin C in patients with neurological diseases and mental disorders

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Citation: Goncharova, P.S., Davydova, T.K.; Zhukova, N.G. Prospects for studying the pharmacokinetics, pharmacodynamics and pharmacogenetics of vitamin C in patients with neurological diseases and mental disorders. *Personalized Psychiatry and Neurology* **2021**, *1 (2)*: 63-82. https://doi.org/10.52667/2712-9179-2021-1-2-63-82

Chief Editor: Nikolaj G. Neznanov, D Med Sci, Professor

Received: 15 August 2021
Accepted: 21 September 2021
Published: 15 November 2021

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Abstract: Ascorbic acid (vitamin C) is a vital nutrient that belongs to the group of antioxidants. Vitamin C plays an important role in the functioning of the central (CNS) and peripheral nervous system (PNS), including maturation and differentiation of neurons, formation of myelin, synthesis of catecholamines, modulation of neurotransmission and antioxidant protection. Neurological diseases and mental disorders are characterized by increased generation of free radicals. At the same time, the highest concentrations of vitamin C are found in the brain and neuroendocrine tissues. It is believed that vitamin C can affect the age of debut and the course of many neurological diseases and mental disorders. However, its potential therapeutic role continues to be studied. The efficacy and safety of vitamin C is likely influenced by the pharmacogenetic profile of the patient, including the carriage of single-nucleotide variants (SNVs), candidate genes associated with vitamin C metabolism in the human body in normal and neuropsychic disorders. The purpose of this thematic review is to update current knowledge about the role of vitamin C pharmacogenetics in the efficacy and safety of its use in neurological diseases (amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Huntington's disease, Alzheimer's disease, etc.) and mental disorders (depression, anxiety, schizophrenia, etc.). Special attention is paid to the possibility of translating the results of pharmacogenetic studies into real clinical practice in neurology and psychiatry.

Keywords: *ascorbic acid; vitamin C; efficacy; safety; pharmacogenetics; amyotrophic lateral sclerosis; multiple sclerosis; Parkinson's disease; Huntington's disease; Alzheimer's disease; depression; anxiety; schizophrenia.*

Introduction

Ascorbic acid (vitamin C, ascorbate) belongs to the group of water-soluble vitamins. In the human body , vitamin C can exist in two forms: reduced form - ascorbic acid (AA), which at a physiological pH value is in the anionic form of ascorbate; oxidized form – oxidized dehydroascorbic acid (DHA), which is the product of two-electron oxidation of (AA). As a result of metabolic processes in the form of single-electron oxidation, an ascorbate free radical can be formed. This type of metabolite can subsequently undergo dismutation with the formation of ascorbate and DHA [1] (Figure 1, 2).

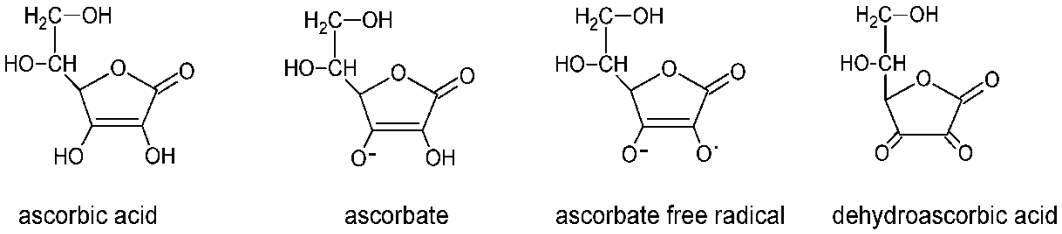

Figure 1. Forms of vitamin C (ascorbic acid) in the human body [2].

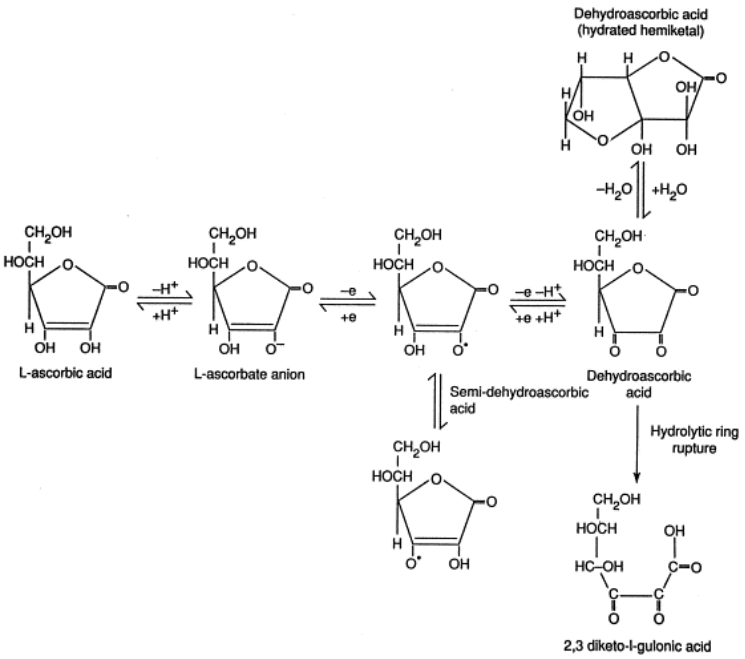

Figure 2. Ascorbate and its oxidation products. Dehydroascorbic acid might exist in multiple forms, although only two are shown here for simplicity. The hydrated hemiketal is proposed to be the favored form in aqueous solutions, [3] but it is unknown which form is found in biological systems. Semidehydroascorbic acid might also have other configurations that are omitted here [4]. Formation of 2,3,-diketogulonic acid by hydrolytic ring rupture is probably irreversible. (Figure from Washko, et al [5]).

It is known that vitamin C is not produced by the intestinal microflora [6]. People are deprived of the ability to synthesize vitamin C independently due to the absence of the enzyme l-gulono-1,4-lactone oxidase, which is an element of the metabolic pathway responsible for the synthesis of ascorbic acid from glucose [1][7]. This is the reason for the strict dependence of the human body on the intake of vitamin C with food (Table 1).

The average plasma levels of ascorbate in a healthy adult population is between 40 and 65 μM. There is no difference between serum and plasma [9][10][11][12][13]. The levels of ascorbate fluctuate with age. They are highest in the category of 6 to 11 years old and then gradually decrease. There is, however, an increase in the population over 60 years old in both men and women [11]. Women have, in general, higher plasma levels than men [11]. The maximal steady-state, long-term ascorbate plasma levels achievable by oral administration are 70–85 μM [14]. The plasma levels increase to this plateau concentration up to doses of about 200–400 mg daily. Higher doses increase plasma levels only minimally [15][16].

Table 1. Vitamin C content in selected fruits, vegetables, and medicinal plants ([8], from modification by P.S. Goncharova).

Latin Name	Family	Vernacular Name	Vitamin C Content
Fruits			
Terminalia ferdinandiana Exell	Combretaceae	Kakadu plum	1360–22,490 [b]
Myrciaria dubia (Kunth) McVaugh	Myrtaceae	Camu-camu	850–5000 [a]
Malpigia emarginata DC.	Malpighiaceae	Acerola	820–4023 [a]
Averrhoa bilimbi L.	Oxalidaceae	Bilimbi	2698 [c]
Averrhoa carambola L.	Oxalidaceae	Star fruit	1626 [c]
Psidium guajava L.	Myrtaceae	Guava	89–980 [a]
Anacardium occidentale L.	Anacardiaceae	Cashew apple	555 [a]
Phyllanthus emblica L.	Phyllanthaceae	Emblic	469 [a]
Ribes nigrum L.	Grossularia-ceae	Black currant	148-310 [a] 60-250 [d]
Actinidia deliciosa (A.Chey.)C.F.Liang et A.R.Ferguson	Actinidiaceae	Kiwi	60-78 [a]
Fragaria virginiana Duchesne	Rosaceae	Strawberry	65 [a]
Citrus x *sinensis (L.)Osbeck.*	Rutaceae	Orange	41–58 [a]
Citrus limon (L.)Osbeck.	Rutaceae	Lemon	30 [d]31 [a]
Citrus reticulata Blanco	Rutaceae	Common manda-rin	27 [a]
Malus domestica Borkh.	Rosaceae	Apple	11–35 [a]
Pyrus commVunis L.	Rosaceae	Pear	7–29 [a]
Vegetables			
Brassica oleracea var. *italica Plenck.*	Brassicaceae	Broccoli	25–130 [a]
Brassica oleracea var. *acephala (DC.)Alef.*	Brassicaceae	Kale	51–120 [a]
Capsicum annuum L	Solanaceae	Pepper	107–154 [a]
Solanum tuberosum L.	Solanaceae	Potato	8–30 [a]
Solanum lycopersicum L	Solanaceae	Tomato	9–17 [a]
Fermented vegetable			
Brassica oleracea var. *capitata (L.)Alef.*	Brassicaceae	Sauerkraut	103–277 [b]
Medicinal plants and herbs			
Hippophaë rhamnoides L	Eleagnaceae	Sea buckthorn	70–1320 [d]
Rosa canina L.	Rosaceae	Rosehip	40–360 [a]
Coriandrum sativum L.	Apiaceae	Coriander	48–98 [a]
Allium schoenoprasum L.	Amaryllidaceae	Chives	93 [a]
Petroselinum crispum (Mill.)Nym.	Apiaceae	Parsley	59 [a]

mg/100 g of [a] fresh weight, [b] dry weight, [c] juice, mg/100 mL of [d] juice.

Table 2. The role of vitamin C in the functioning of the nervous system.

Nutrient	Function in the central nervous system	Authors
Vitamin C (ascorbic acid)	Participation in redox processes (protection from O2 free radicals). Participation in protein synthesis (amidation of peptides). Participation in the synthesis of myelin. Synaptic potentiation. Neuroprotection (protection from the action of excitatory neurotransmitters - glutamate). Participation in regeneration processes. Participation in energy processes. Participation in the absorption of calcium and iron. Participation in the regulation of neuroimmune response (influence on resistance to viruses, bacteria and parasites). Slowing down the aging process and protection from oncopathology. Increased effect of adrenaline (antistress effect). Participation in the regulation of emotional reactions, cognitive functions. Participation in cholesterol metabolism. Participation in the synthesis of collagen. Influence on mental and physical performance. Influence on the equilibrium function. Increased resistance to adverse environmental factors (infections, exposure to low doses of chemicals, ionizing radiation, reduction of adverse reactions of a number of drugs).	[25][26][27][28]

Concentrations up to 220 μM can also be reached for a short time, but this requires a maximum tolerable dose of 3 g every 4 hours [17]. It is well known that smoking affects ascorbate plasma levels negatively [10][11]. Smoking decreases the plasma level of ascorbate on an average by 25–50% [18][11][13]. Ex-smoking seems to slightly decrease the levels as well [18][10]. These lower plasma levels can be at least partly accounted to the increased oxidative stress caused by smoke. The need for ascorbate in smokers is higher, but the available studies suggested different recommendations ranging from 35 to 200 mg of additional vitamin C/day needed for smokers [18]. The plasma levels of DHA are very low in healthy humans, while that of an ascorbyl radical are undetectable [19, 20,21]. The recommended daily dose of vitamin C was set at 60 mg, but smokers have a higher daily dose of vitamin C - up to 140 mg [22]. According to current recommendations, the daily dose of vitamin C is 75 mg for women and 90 mg for men. This dose should be increased by 35 mg per day for men and women who smoke [6][23][24].

The role of vitamin C in physiological processes in the human body and in neurological diseases and mental disorders is being actively studied. This is due to the important role of vitamin C for the proper development and functioning of the central nervous system (CNS) and peripheral nervous system (PNS) (Table 2).

Vitamin C plays an important role in neurotransmission, the maturation and functioning of neurons [29] in children, adolescents and adults, including the impact on the age of the onset and progression of neurological diseases; the development of epilepsy [30][31],the development of Alzheimer's disease [31][32][33][34][35]the development of Parkinson's disease (PD) [36][37][38][39][40][41][42], Huntington's disease (HD) [43][44][45] multiple sclerosis (MS) [46][47] [48][49.], amyotrophic lateral sclerosis (ALS) [50][51][52.][53] mental disorders: depression [54][55][56] anxiety [57][58][59], schizophrenia [60][61][62]. In addition to this role, vitamin C is involved in numerous non-

oxidative processes: biosynthesis of collagen, carnitine, tyrosine, peptide hormones, myelin [2].

However, the efficacy and safety of vitamin C in the above diseases and mental disorders is contradictory. For example, numerous studies have been conducted on the role of nutrients in the development of ALS, including vitamin C [63]. In some studies, the effect of vitamin C on the development and course of ALS has been confirmed [64][65][66][67], in others it is refuted [68][69][70][71][72] (Figure 2).

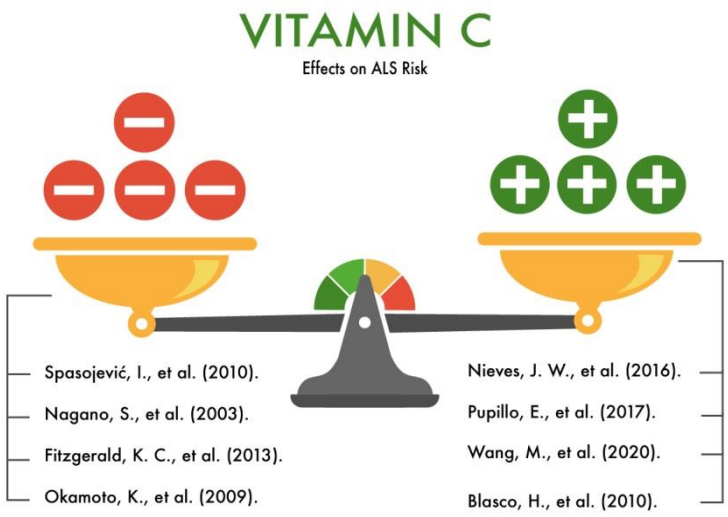

Figure 3. The effect of vitamin C on the risk of developing amyotrophic lateral sclerosis (ALS). [72]

Probably, such contradictory results are due to the individual pharmacogenetic profile of patients.

Objective

The purpose of this thematic review is to update current knowledge about the role of vitamin C pharmacogenetics in the efficacy and safety of its use in neurological diseases and mental disorders. Special attention is paid to the possibility of translating the results of pharmacogenetic studies of vitamin C into real clinical practice in neurology and psychiatry.

Materials and Methods

We conducted a search for full-text English and Russian-language publications in PubMed, Springer, Clinical keys, Google Scholar and E-Library databases using keywords and their combinations: ascorbic acid; vitamin C; efficacy; safety; pharmacogenetics; amitrophic lateral sclerosis; multiple sclerosis; Parkinson's disease; Huntington's disease; Alzheimer's disease; depression; anxiety; schizophrenia. We analyzed all available studies, the results of which were published in 2010-2020. 324 publications that corresponded to the purpose of this review were analyzed. In addition, studies of historical interest were included in the review. Despite a comprehensive search, it is possible that some publications could have been missed.

Results

Absorption of Vitamin C

To provide tissues with ascorbate, people should take vitamin C with food or dietary supplements (dietary supplements) and absorb it in the gastrointestinal tract (gastrointestinal tract). Since ascorbic acid and DHA are transported in *vivo*, it is important to consider the intestinal absorption of both forms.

Ascorbate in its reduced form makes up the majority (80-90%) of vitamin C in food [73]. Ascorbate is absorbed in the human intestine by the Na+-dependent active transport system [74]. Absorption is most effective in the proximal part of the intestine [75].

It is not known whether there are individual differences in ascorbate absorption. There is a possibility that the transport of vitamin C in the gastrointestinal tract is regulated. In guinea pigs, pre-feeding with large doses of ascorbate reduced transport through the isolated intestinal mucosa [76]. However, this has not been investigated in humans [77].

The absorption of DHA in the gastrointestinal tract in humans has not been sufficiently studied. In an animal model (guinea pig), it was shown that the absorption of DHA is a Na+-independent, saturating process [78]. Most of the DHA is immediately restored when crossing the serous membrane and is present in the form of ascorbate [79].

The absorption of DHA is lower than that of ascorbate [80]. It is unknown whether the microbiota in the gastrointestinal tract affects the reduction of DHA to ascorbate or hydrolysis to diketogulonic acid.

It is unclear which mechanisms physically ensure the intersection of intestinal membranes: ascorbate or DHA or both. According to the recirculation of ascorbate, the data suggest that both species are absorbed, but by different mechanisms [81].

Absorption is determined clinically using pharmacokinetic principles of bioavailability. True bioavailability is defined as an increase in the amount of a substance in plasma after oral administration compared with an increase in the amount of a substance in plasma after intravenous administration of the same dose [82].

The bioavailability of ascorbate is most important because it is the dominant substrate in foods and dietary supplements and the dominant (if not only) substrate in blood plasma. It is important to investigate the true bioavailability at different doses of ascorbate [83][84]. Based on a five-component pharmacokinetic model, the bioavailability of ascorbate in liquid solution administered Fasting was 90% for ≤ 200 mg, 73% for 500 mg and 49% for 1250 mg [83] [84].

However, these results are not confirmed at ascorbate doses < 200 mg, but can be refined using a new model, taking into account changes in its clearance [84].

The effect of various foods on the bioavailability of ascorbate is still largely unknown. The true bioavailability of ascorbate for various foods has not been determined. Studies examining relative bioavailability have found a small difference in absorption between pure ascorbate and ascorbate in foods [85], with the exception of one study that showed that the relative bioavailability of ascorbate increased by 35% when vitamin C was accompanied by the intake of citrus extract [86].

Vitamin C Transport

Ascorbate is present in the blood at concentrations of 5-90 microns in healthy people [87], whereas DHA is present only in very low concentrations (< 2% ascorbic acid) or absent altogether [12] [88]. Ascorbate in plasma and serum is available to tissues and cell carriers directly, without intermediate connection with protein [89].

Different types of cells in the blood carry both ascorbate and DHA in *vitro* [90]. Although the rate of DHA transport is higher than the rate of ascorbate transport, in all these cells the concentration of DHA present in the blood as a substrate is insignificant in most cases.

The content of ascorbate in erythrocytes [91] is difficult to interpret, since ascorbate is easily oxidized by iron and/or hemoglobin. The concentration of ascorbate in

erythrocytes is probably less than in plasma. Ascorbate accumulates in mM concentrations in neutrophils, lymphocytes, monocytes and platelets [83][90].

Levine M. et al. the relationship between the consumption of ascorbate in a wide range (30-2500 mg per day) and the concentration of ascorbate in plasma and tissues was studied [83].

The absorption of vitamin C takes place mostly in the distal ileum. Plasma ascorbate concentrations, depending on the dose, demonstrate the kinetics of saturation of the sigmoid colon. The transport to enterocytes is mediated by SVCT1 (sodium-dependent vitamin C transporter 1, solute carrier of the family of ascorbate transporters, SLC23A. The first dose of ascorbate behind the steep section of the curve was 200 mg per day. The most noticeable changes in plasma ascorbate concentration were observed between 30 and 100 mg/day. Consequently, variations in vitamin C intake in this range can significantly affect the availability of ascorbate in tissues. Doses above 400 mg/day led to a slight further increase in the concentration of ascorbate in plasma, and absorbed doses were almost completely excreted in the urine [83].

So, ascorbate and DHA are transported through cell membranes. Ascorbate transport demonstrates saturation kinetics, as shown in normal human cells. In most cases, the transport of ascorbate is facilitated by Na+, depending on organs and tissues [92]. Ascorbate transport requires metabolic energy [93][94] with stoichiometry for Na+ [95]. However, some tissues demonstrate sodium-independent ascorbate transport [96], but these results are doubtful due to the lack of adequate control data, low transfer rate or nonspecific analyses. The apparent affinity of ascorbate transport (Km) has been determined in human fibroblasts, neutrophils, lymphocytes and osteoblasts in ranges from 5-20 microns [92][93][94]. The proteins responsible for ascorbate transport have not been sufficiently studied.

When transported to cells, DHA is enzymatically converted to ascorbate by glutathione (GSH), thioredoxin, or nicotinamide adenine dinucleotide phosphate (NADP) [97].

Since GSH is an important cofactor in the regeneration of ascorbate [98], the effect ofPEG-AOase [poly(ethylene glycol)]-AOase on GSH status in tissues has been studied by Kasahara. E. et al. [97].

DHA transport is mainly independent of Na+ in animal and human tissues [99] [90][92] and does not require metabolic energy. The proposed mechanism is one of the cellular traps. Upon entering the cells, DHA is immediately restored to ascorbate, which provides an effective gradient of DHA through the cell membrane [90].

The apparent Km reported for DHA transport is usually much higher than that of ascorbate and ranges from 0.75 to 3.7 mM in human neutrophils, fibroblasts, and human leukocyte antigen (HL60) cells [100][101].

The interaction between DHA transport and glucose transport has been studied for many years [102]. Kinetic data suggest that in some tissues DHA can be transported by the same transporters as glucose [103]. Seven isoforms of the glucose transporter (GLUT 1-5, SGLT1 and SGLT2) can participate in the transport of DHA [100][104], which differ in affinity to the substrate and distribution in human tissues.

The cellular model shows that glucose transporters GLUT1 [105] and GLUT3 [106] act as DHA transport proteins with affinity similar or lower than glucose affinity (1-2 mM) [106]. GLUT4 in humans also mediates DHA transport, but 2-3 times less than for glucose [106]. GLUT2, GLUT5, and SGLT1 in humans were unable to transport DHA. GLUT1-5 and SGLT1 did not tolerate ascorbate [106]. However, according to other studies, two components of DHA transport have been shown, although only one of which could be calculated (transport KM 35.5 microns) [107].

Ascorbate absorption is not linear. Bioavailability decreases with an increase in the dose of vitamin C by: 100% at a low dose of vitamin C (200 mg); 73% at an average dose of 500 mg; 50% at a dose of 1.25 g of vitamin C per day [108].

An interesting aspect is the transportation of ascorbate to the central nervous system. Ascorbate is known to be transported to the cerebrospinal fluid in the choroidal plexus via SVCT 2. Ascorbate can pass through the blood-brain barrier in the form of DHA using

the glucose transporter GLUT1 [18][20][109]. The penetration of DHA into the brain seems to be much more intense and rapid than ascorbate [110]. Physiologically, this transport is of secondary importance. DHA is unstable and has very low plasma levels, so it competes with physiologically low millimolar plasma glucose levels for these carriers. The absorption of ascorbate in this form via GLUT1 is controversial [20][111]. Moreover, the absence of SVCT2 in rodents leads to a very low level of ascorbate in the brain, which clearly emphasizes the importance of this transport for the brain [112]. Ascorbate uptake by neurons is very intense and is mediated mainly by SVCT2. GLUT1/3 may also facilitate the transport of DHA to neurons. Neurons have very high intracellular concentrations of ascorbate, which can reach 10 mM. At the same time, the concentration of ascorbate in the glia is similar to other cells of the body. The level of ascorbate in the cerebrospinal fluid is about 200 microns. This is four times higher than the average plasma ascorbate level. Ascorbate appears to be crucial for brain functions. The level of ascorbate in the central nervous system is important for the development of many neurological diseases and mental disorders [109] (Table 2). The absence of SVCT2 is incompatible with life [112][113].

SVCT2 expression increases after experimental vascular brain injury [20]. However, this mechanism needs to be studied in neurodegeneration and mental disorders.

Tissue Accumulation of Vitamin C

Ascorbate accumulates in various tissues of the human body in different concentrations. The maximum accumulation of ascorbate (ascorbate / 100 g of tissue) is described in the adrenal glands and pituitary gland (30-50 mg / 100 g). In addition, high accumulation of ascorbate is observed in other regions of the brain, lens, liver, spleen, pancreas and kidneys (10-30 mg /100g) [114].

In humans, it is difficult to study the relationship between vitamin C intake with food and dietary supplements and the concentration of ascorbate in tissues and organs. Tissue samples are difficult to obtain, since the degradation of ascorbate in tissue samples occurs very quickly. This makes laboratory tests difficult. The distribution and accumulation of ascorbate in various tissues (brain, heart, spleen, leukocytes, adrenal glands) was studied on an animal model (guinea pigs that do not synthesize ascorbate) [115]. As a result, it was shown that the accumulation of ascorbate in the tissues of guinea pigs and humans is similar [114].

The half-life of ascorbate in specific human cells or tissues under conditions of minimal vitamin C intake has not been sufficiently studied. Based on mathematical modeling of urinary excretion of radioactively labeled ascorbate, estimates of ascorbate loss from the theoretical total body pool of 2.6 to 4.1% per day were made [116]. However, these estimates do not provide information about the accumulation of ascorbate in specific tissues. In circulating mononuclear leukocytes, the half-life of ascorbate was approximately 30 days [117].

Factors that probably affect the half-life of intracellular ascorbate include initial intracellular and plasma extracellular concentrations [81].

It is possible that DHA is not found in appreciable amounts in human tissues [107]. When radiolabeled ascorbate and DHA were administered to guinea pigs, there were clear differences in tissue distribution and absorption rate [118]. Ascorbate was rapidly accumulated by the adrenal glands and pituitary gland, lungs, liver, kidneys, bones and skin. DHA remained mainly in blood plasma and blood cells. Even after the injection of DHA, all the radioactive label isolated from the tissue was found in the recovered form. Since DHA is rapidly transported to and restored by blood cells, it is probably inaccessible to most tissues through blood circulation. This concept is confirmed by the release of glutaredoxin from erythrocytes [119] and neutrophils [120], as well as the high ability of erythrocytes to restore DHA, chemically mediated through GSH [121].

Unlike most human tissue cells, circulating blood cells can be easily isolated. This makes it possible to study the concentration of ascorbate in blood cells and to study the relationship between vitamin C intake and the cellular concentration of ascorbate in humans. However, well-controlled studies of the relationship between the accumulation of

ascorbate in circulating blood cells and human dietary habits are not enough. Some researchers have suggested that erythrocytes and platelets contain the highest proportion of ascorbate among blood cells due to their large number [122]. However, as noted above, the determination of ascorbate in erythrocytes is problematic due to the presence of very large amounts of highly reactive heme iron, which can easily oxidize ascorbate during sample preparation or storage. To date, a rigorous analysis of the ascorbate content in erythrocytes is not available.

The National Institutes of Health (NIH) study was devoted to the study of the relationship between the daily dose of vitamin C and the accumulation of ascorbate in lymphocytes, neutrophils and monocytes [87]. The level of intracellular ascorbate in these blood cells was lower than that in comparison with plasma when taking vitamin C 100 mg / day. The increase in intracellular ascorbate concentration (up to 1.4 mmol) was 14 times higher compared to plasma.

Vitamin C Metabolism

The relative proportion of vitamin C metabolism products in the human body is not clear, but probably depends on the daily dose, ascorbate replenishment status and other unknown factors. In one study, patients received [14C] ascorbate intravenously, metabolites in urine were measured: 40% - oxalate; 20% - diketogulonic acid; 2% DHA; and the rest - in an unknown form [123]. The inaccuracy of the analysis and artifacts are due to the decomposition of ascorbate during processing that led to an unclear interpretation of the results obtained.

It remains unclear which factors may regulate the production of ascorbate metabolites. In the production of two main metabolites (oxalate and diketogulonic acid), DHA is used as a precursor [124], although DHA itself is not detected in urine [125]. Factors that increase the oxidation of ascorbate to DHA can theoretically increase the irreversible production of metabolites and, thereby, lead to an increase in the utilization of ascorbate. With oral or intravenous administration of vitamin C to volunteers at doses of 500 and 1250 mg, the metabolites of ascorbate were almost completely explained by urinary excretion of ascorbate [87]. However, oxalate excretion was maximal when taking 1 g of ascorbate per day. At this dose, the amount of oxalate recovered was <10% of the ascorbate recovered. Measurements of oxalate in urine reflect its metabolism from all sources.

For a stationary state with doses of vitamin C ≥ 500 mg, most of the ascorbate in healthy people is excreted in the urine. In doses of vitamin C < 60 mg per day, ascorbate itself is not excreted, and only metabolites, mainly oxalate, are excreted in the urine.

Ascorbate is oxidized by various enzymatic and non-enzymatic reactions [126]. In particular, ascorbate can be consumed in chemical reactions in which oxidants are reduced. The proposed data support the hypothesis that oxidative processes regulate ascorbate catabolism in humans, although there is currently no direct evidence. Other antioxidants are also present in plasma, including uric acid, tocopherols and ubiquinone. However, ascorbate can preferably be oxidized and can play an important role as the first protection of the central nervous system and the PNS from oxidative stress [127].

The dissociation constant (pKa) of ascorbic acid is 4.1–4.2. Consequently, it is completely present in the form of monoanion - ascorbate at a physiological pH value. [128][129][111].

This form cannot directly penetrate cell membranes. For this reason, carriers are key players in the pharmacokinetics of vitamin C. Ascorbate is absorbed by cells through SVCT2, which is a close analogue of SVCT1, with which it has 65% sequence homology. SVCT2 is largely expressed in most organs. SVCT1 expression is limited. In addition to the intestine, it is expressed in the liver, lungs, skin, ovaries, prostate and kidneys. By analogy with SVCT1, SVCT2-mediated ascorbate transport is unidirectional and uses an electrochemical sodium gradient. Two Na ions are necessary for the transport of ascorbate by both transporters. SVCT2 has an affinity for ascorbate 2-10 times higher than SVCT1. However, Vmax is clearly lower. This implies a lower ability to transport ascorbate, but with a higher sensitivity. Transport also works at lower concentrations of ascorbate. This

is consistent with the physiological need for a higher ability of SVCT1 to transport vitamin C from the diet and the functions of SVCT2 to provide cells with ascorbate even at its low plasma level [18][20][113][130][131].

SVCT2 provides a significant concentration gradient of plasma tissues. Intracellular levels of vasorbate are much higher than plasma levels. Ascorbate reaches a concentration of 0.5-5 mM in most cells with the exception of erythrocytes that do not express SVCT2. Therefore, the cytosolic level of ascorbate reflects plasma levels and is about 50 microns [15][18][111].

In contrast to the maximum level of ascorbate in plasma, the maximum concentration of ascorbate in different types of white blood cells (lymphocytes, neutrophils, monocytes) was achieved at a dose of 100 mg per day. Higher doses of vitamin C consumed in men did not significantly increase intracellular ascorbate levels [15]. A possible cause may be the saturated kinetics and active transport of ascorbate through SVCT2 with a Km of about 60-70 microns, which is an approximate plasma level associated with daily intake of 100 mg of vitamin C [14.]. In women, this was not confirmed: the saturated doses of vitamin C were 200-400 mg per day. This corresponded to doses of vitamin C, which provided the maximum stable level of ascorbate in plasma [132]. Physiologically high levels of ascorbate (2-10 mM) are found in neurons and endocrine cells, in particular, in the adrenal glands and pituitary gland. This is probably due to the synthesis of hormones and neurotransmitters [19][109]

Ascorbate has a slight tendency to exit cells, probably due to its hydrophilic nature and negative charge at physiological pH [109]. In extracellular fluid, ascorbate concentrations are slightly higher than in plasma [21].

DHA is not similar to glucose, but forms a bicyclic hemiketal that resembles glucose [133] and has a high affinity for glucose transporters GLUT1 and GLUT3 (GLUT4 may participate, but GLUT2 and GLUT5 do not) [131]. These transporters provide easy diffusion and are therefore bidirectional.

Since the concentration of DHA in plasma is low, the oxidized form of vitamin C in cells is probably rapidly restored to ascorbate. This is most typical for red blood cells. Recovery is a crucial step as DHA is not very stable. DHA has a half-life of about 6 minutes and decomposes to 2,3-diketo-1-gulonic acid and thus loses vitamin C activity [19][109][111].

Apparently, there are additional pathways mediating the recovery of DHA to ascorbate. These include slow non-enzymatic reduction by glutathione (GSH), enzymatic reduction by a pair of enzymes (for example, glutaredoxin, omega 2 glutathione transferase or thioredoxin reductase). The first two enzymes require GSH for their activity [109][128]. Erythrocytes are very active in providing DHA metabolism pathways [18][19]. After converting DHA to 2,3-diketo-1-gulonic acid, metabolism can follow several scenarios. It can be decarboxylated, and the products can enter the pentose phosphate shunt using a pair of reactions [134]. In addition, 2,3-diketo-1-gulonic acid can decompose into erythrulose and oxalate. This reaction is accelerated by bicarbonate [128]. The role of these metabolic pathways in the development of neurological diseases and mental disorders has not been sufficiently studied.

Excretion of Vitamin C

In humans, ascorbate is filtered in the glomeruli and reabsorbed in the proximal tubules of the kidneys due to the active transport process [134]. In humans, the upper range of ascorbate concentration in the blood is limited by renal reabsorption [135]. The maximum rate of tubular ascorbate reabsorption was determined in men and women of different ages and proved to be relatively constant between groups at approximately 1.5 mg/100 ml of glomerular filtrate [136].

As in the intestine, ascorbate transport in the renal tubules is Na+-dependent [134]. Ascorbate transport in brush border vesicles from the renal cortex is saturable, potentially sensitive, and partially inhibited by glucose [137]. The reabsorption of ascorbate in the kidneys is presumably associated with the concentration of ascorbate in the tubules. It is

unknown whether ascorbate reabsorption can be regulated by other mechanisms. It is also unknown whether ascorbate is secreted into the renal tubules.

It was believed that the threshold dose of ascorbate for urinary excretion is a dose close to satiating, and the current recommended diet for vitamin C is partially based on this concept [138]. A study of vitamin C deficiency replacement showed that ascorbate is excreted in the urine of volunteers who consistently received vitamin C at a dose of 60 mg per day [139]. This data was used to establish the currently recommended intake of vitamin C in the diet at the level of 60 mg per day [138].

The threshold of ascorbate excretion in urine was studied in a NIH study [87]. Ascorbate excretion was measured with a stable intake of vitamin C at a daily dose of 30 - 1250 mg. As a result, it was shown that ascorbate appears in urine only at doses of vitamin C ≥ 100 mg / day, [87] [140], which corresponds to an average plasma ascorbate concentration of 55–60 μM. At this dose, lymphocytes, neutrophils and monocytes were completely saturated, and plasma was saturated by about 70%. The total saturating dose of ascorbate was 1000 mg per day of vitamin C.

Unlike ascorbate, DHA transport in isolated renal tubules is Na+-independent and insensitive to transmembrane electric potential difference and does not concentrate against the gradient [141][142]. Transported DHA is rapidly restored to ascorbate in isolated renal tubules of rats and guinea pigs [143]. The transport of ascorbate and DHA through the basolateral membrane of nephrons is an Na+-independent process with a comparable rate [143]. There is no data on renal excretion or reuptake of DHA in *vivo*, since measurable amounts cannot be detected in plasma.

Determination of DHA in urine is associated with the same methodological difficulties as in plasma. Most likely, DHA is present in urine in very small amounts or is absent altogether. Large amounts of DHA in urine are probably the result of an experimental artifact [125].

In humans, urine is the main and possibly the only way to excrete ascorbate and ascorbate metabolites. Metabolites of known structure found in urine using ascorbate labeled with 14C include DHA, diketogulonic acid, oxalate, ascorbate-2-sulfate, and methyl ascorbate [144]. In the human body, approximately 90% of ascorbate and ascorbate metabolites are excreted in the urine.

There is little quantitative information on the relationship between ascorbate replenishment status or vitamin C intake and the formation and excretion of ascorbate metabolites in human urine. Some studies have shown that up to 30% of ascorbate administered at doses > 180 mg/day is excreted as CO2. However, the data obtained were attributed to presystemic bacterial or chemical degradation of ascorbate in the gastrointestinal tract [144][145].

Qualitative data indicate that the formation of a constitutive amount of metabolites can occur at any doses of vitamin C [116].

At the same time, impaired renal function can seriously affect the excretion of ascorbate. In healthy people, the entire plasma ascorbate content is filtered and reabsorbed in the kidneys approximately once an hour. It is not known whether there are mechanisms regulating these processes. In patients with renal insufficiency, an inverse correlation was observed between creatinine clearance and ascorbate excretion [146]. It is not yet possible to draw definitive conclusions from these observations. We have not found any differences between different types of kidney diseases and the recommended doses of vitamin C for neurological diseases and mental disorders.

Radioactively labeled vitamin C, administered to healthy people, showed that most of the ascorbate amount is excreted by the kidneys. Only less than 1% of ascorbate was excreted in faeces. Ascorbate was not actually exhaled as CO2. About 20% of ascorbate excretion in urine falls on non-metabolized ascorbate, the remaining 20% on 2,3-diketo-1-gulonic acid, only 2% DHA. At the same time, on average 44% of the metabolites were excreted as oxalate [147].

Ascorbate is effectively and richly reabsorbed from the urinary tract. The SVCT 1 transporter plays an important role, as has been documented in knockout Slc23a1 -/ - mice

[130][148][149]. Excess ascorbate is effectively excreted in the urine to maintain the homeostatic level of ascorbate in plasma.

Table 3. Candidate genes and their single-nucleotide variants affecting vitamin C metabolism in the human body.

Gen	Chromosome Location	Protein / Enzyme	Changes in vitamin C metabolism	References
SLC2A1	1p34.2 (10 exons)	Glucose transporter 1 (GLUT1) or solute carrier family 2, facilitated glucose transporter member 1 (SLC2A1)	Transport	[100][104] [105]
SLC2A2	3q26.2 (12 exons)	Solute carrier family 2, facilitated glucose transporter member 2 (SLC2A2)	Transport	[100][104]
SLC2A3	12p13.31 (10 exons)	Glucose transporter 3 (GLUT3) Solute carrier family 2, facilitated glucose transporter member 3 (SLC2A3)	Transport	[106]
SLC2A4	17p13.1 (11 exons)	Glucose transporter 4 (GLUT4) Solute carrier family 2, facilitated glucose transporter member 4 (SLC2F4)	Transport	[106] [100][104]
SLC2A5	1p36.23 (13 exons)	Glucose transporter 5 (GLUT5) Solute carrier family 2, facilitated glucose transporter member 5 (SLC2A5)	Transport	[100]
SLC5A1	22q12.3 (16 exons)	Sodium-dependent glucose cotransporters/sodium-glucose linked transporter (SGLT1)	Transport	[100][104]
SLC5A2	16p11.2 (14 exons)	Sodium-dependent glucose cotransporters/sodium-glucose linked transporter (SGLT2)	Transport	[100][104]
SLC23A1 (SVCT1)	5q31.2 (17 exons)	Solute carrier family 23 member 1 (SLC23A1)	Absorption Excretion Transport Metabolism	[155] [156] [157]
TGFB1	19q13.2 (7 exons)	L-buthionin-(S,R)-sulfoximine Transforming growth factor beta 1 (TGFB1)	Metabolism	[158] [159]

IGF1	12q23.2 (7 exons)	Insulin like growth factor 1	Metabolism	[160]
SLC23A2 (SVCT2)	20p13 (18 exons)	solute carrier family 23 member 2	Transport Metabolism	[161][162][163]

The player responsible for saturated ascorbate reabsorption is, as in the gastrointestinal tract, the SVCT1 transporter, which is expressed on the brush border of the proximal tubules of the kidneys. Since the pH of urine is lower, passive diffusion of ascorbate has been suggested. However, this mechanism plays a secondary role, if at all [18][20].

The saturable reabsorption mechanism is responsible for maintaining the concentration of ascorbate in plasma along with absorption. When vitamin C is consumed in daily doses of 30-60 mg , ascorbate is practically not excreted in the urine for 24 hours . At the same time, a dose of 100 mg of vitamin C leads to the release of 25% of the dose of vitamin C. When vitamin C is consumed at a dose of 500 mg or higher, ascorbate is almost completely eliminated from the body [15]. The Michaelis km constant for renal reabsorption of vitamin C in relation to its plasma levels was 33 microns. This roughly corresponds to the maximum levels of ascorbate in plasma [150]. The half-life of ascorbate is usually about 2 hours [18].

Genetic Polymorphism Of Candidate Genes For Vitamin C Metabolism

The influence of single-nucleotide variants (SNVs) of candidate genes involved in the exchange (absorption, transport, metabolism and excretion) of vitamin C and affecting the pharmacokinetics of ascorbate has been actively studied in recent years. This is due to the fact that the effectiveness and safety of vitamin C use in patients varies even within the same ethnic group. Knowledge of genetic predictors of changes in vitamin C metabolism is important to take into account when treating patients with neurological diseases and mental disorders.

The most studied are the SNVs of the *SLC23A1* and *SLC23A2* genes in various diseases in humans [19][129]. The strongest evidence is that a decrease in circulating ascorbate levels was associated with the carriage of several common SNVs of the *SLC23A1* gene due to a decrease in renal ascorbate reabsorption. However, an increase in the level of ascorbate in plasma and in the central nervous system is rarely described [148][151][152]. It is known that these SNVs are more common in populations of Africans and African Americans than in other populations, while the SNVs of the Slc23A2 gene have a similar frequency in populations of Europeans and Africans [148][151][153].

Some SNVs of the *SLC23A1* gene have been characterized as synonymous and non-synonymous SNVs with the greatest diversity among representatives of the African population producing proteins with lower functionality. In the case of the *SLC23A2* gene, all studied SNVs were synonemic [148][152].

The effect of carrying SNVs candidate genes on vitamin C metabolism is additive, depending on the genotype. In addition, it is important to take into account the effect of the dosage of the allele (additive effect), which was also previously described. More than a hundred less common or rare SNVs genes have been described. Their population frequency is unknown. Consequently, the global effect of SNVs of these candidate genes on the level of ascorbate in plasma and the central nervous system, as well as their association with neurological diseases and mental disorders, needs further study [129][152][154].

In addition, other candidate genes associated with changes in the absorption, transport, metabolism, accumulation and excretion of ascorbate, DHA and their metabolic products are promising. Associative genetic studies can help us choose a personalized dose and regimen of nutrients containing ascorbate, as well as to develop an individual

diet for patients with a wide range of neurological diseases and mental disorders, including neurodegenerative diseases (primarily ALS).

Conclusions

This thematic review expands the knowledge of neurologists and psychiatrists about the metabolism of ascorbic acid as a nutrient that can potentially influence the onset and course of various neurological diseases and mental disorders. Analyzed studies indicate that prescribing high doses of vitamin C is often not justified, even in healthy people. Careful choice of the dose and regimen of vitamin C intake is necessary for patients with an unfavorable pharmacogenetic profile, in particular in carriers of SNVs candidate genes encoding ascorbate and DHA transporter proteins through the blood-brain barrier, the membrane of neurons and the membrane of renal tubule cells. Despite numerous studies on the important role of vitamin C in the development and function of the central nervous system and PNS [72], the role of ascorbate pharmacogenetics has not been sufficiently studied. This is the reason for local and large interregional associative genetic studies of vitamin C pharmacogenetics in various ethnic groups and climatageographic regions in patients with neurological and mental disorders having different dietary habits.

Author Contributions: Conceptualization, P.S.G. and T.K.D.; methodology, P.S.G; software, P.S.G.; validation, T.K.D.; formal analysis, P.S.G.; investigation, P.S.G; resources, T.K.D.; data curation, T.K.D..; writing—P.S.G.; writing—T.K.D. and P.S.G.; visualization P.S.G.; editing – N.G.Z.; project administration, P.S.G.

All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement. Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Acknowledgments: The authors would like to thank Anna V. Dyuzhakova (humsterzoa@gmail.com) for preparing Figure 3.

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