On mathematical modeling of vitamin C role in the tripartite synapse, calcium waves, and neurodegenerative diseases

Manfred Sneps-Sneppe

***Abstract*—The main goal is to initiate the young mathematicians in this mysterious world of vitamin C role in our brain. Information that may be useful for tripartite synapse mathematical modeling is collected. The volume of this knowledge is enormous and constantly growing. As a starting point, one needs to understand how ascorbic acid (vitamin C) changes during synaptic activity and how it is astrocyte-mediated recycling from oxidized ascorbic acid back. The paper contains elementary insight into neurons, action potential, and the energy supply to the brain. Three mathematical models of calcium waves are briefly mentioned, and the role of vitamin C in calcium channel regulation is explained. The conclusion contains a discussion about the birth of a new science – neuro-gastroenterology.**

***Keywords:* vitamin C, mathematical modeling, tripartite synapse, calcium waves, neurodegenerative diseases, leaky gut**

I. Introduction

The idea for this paper arose after my studies on the history of science in cancer treatment, specifically about Linus Pauling's [1]and Manfred von Argenne's [2] lives, and the main goal is to initiate the young mathematicians in this mysterious world.

Vitamin C. Let's add a few words about vitamin C, discovered in 1912, isolated in 1928, and in 1933 was the first of vitamins to be chemically produced. For its discovery, Albert Szent-Györgyi **(**1893-1986), a Hungarian biochemist, was awarded the 1937 Nobel Prize in Physiology or Medicine.

Linus Pauling (1901-1994) was an American theoretical physical chemist, who became the only person to have won two unshared Nobel Prizes. His first prize (1954) was awarded for research into the nature of the chemical bond, in molecular structure studies (in simple terms, for an unknown insight into the microworld); the second prize (1963) – Nobel Peace Prize – documented his efforts to ban the testing of nuclear weapons (in other words, for an effort to change something in the macro world, in geopolitics). In his book “Vitamin C and the Common Cold”, published in 1970, Pauling recommended high doses of vitamin C to prevent colds or lessen their symptoms based on his knowledge of molecular biology. Until the end of his life, Pauling maintained his belief in vitamin C, despite the objections of many medical authorities, for treating many diseases, including cancer. Only in 2015, 20 American scientists [3] proved that vitamin C molecules can kill cancer cells. Shortly speaking, they managed the complex path of the vitamin C molecule from the blood capillary to the cancer cell, further - to its nucleus, and its damage, which leads to its death. This fact scientifically substantiated Pauling's hypothesis, the truth of which many practical doctors did not doubt all these 50+ years, and gained additional evidence during the COVID [30]. Therefore, Pauling’s hypothesis turned out to be correct.

Warburg effect and lactate. In the 1920s, Otto Warburg (1883-1970, Nobel Prize in Physiology or Medicine in 1931) observed for the first time that tumors consume more glucose than surrounding normal tissue, leading him to propose the phenomenon of aerobic glycolysis, wherein glucose can be fermented to produce lactate instead of carbon dioxide, even in the presence of oxygen; this phenomenon is now known as the Warburg effect [4]. Below lactate is discussed in the context of energy supply for the brain.

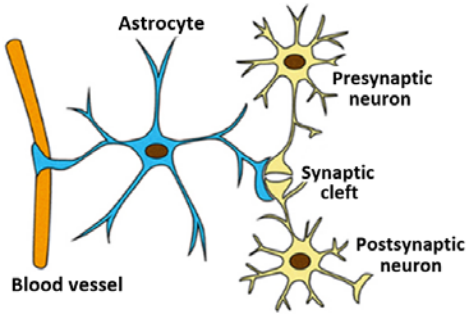

Fig. 1. Tripartite Synapse Scheme.

Our goal is to collect together the maximum amount of information that may be useful for tripartite synapse modeling (Fig. 1). The volume of this knowledge is enormous and constantly growing. As a starting point, we need to understand how ascorbic acid (Asc) changes during synaptic activity and how it is astrocyte-mediated recycling from oxidized ascorbic acid (DHasc) back to Asc [5]. The remainder of this paper is the following. Section 2 contains elementary insight into neurons and action potential. In Section 3 we consider energy supply for the brain. Sections 4 and 5 are about mathematical modeling. In Section 6, the role of vitamin C in calcium channel regulation is discussed. In conclusion, in Section 7, we talk about the birth of a new science neuro-gastroenterology.

M. Sneps-Sneppe – independent researcher, Ventspils, Latvia (e-mail: manfreds.sneps@gmail.com).

II. NEURONS AND ACTION POTENTIAL

Synaptic transmission is the process by which one neuron communicates with another. Information is passed down the axon of the neuron as an electrical impulse known as an action potential (Fig. 2). Neurons communicate with other cells via synapses, that commonly use chemical neurotransmitters to pass the electric signal from the presynaptic neuron to the target cell through the synaptic gap.

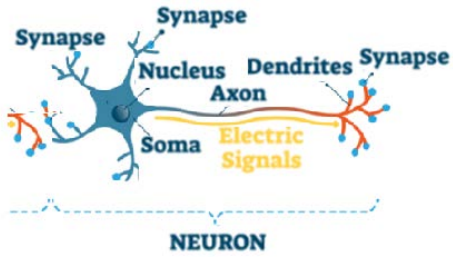

Fig. 2. Neuron communication scheme.

The human brain has some 8.6 x 10^{10} (eighty-six billion) neurons. Each neuron has on average 7,000 synaptic connections to other neurons, totaling from 100 to 500 trillion synapses. Every cubic millimeter of cerebral cortex contains roughly a billion of them.

Astrocytes are characteristic star-shaped glial cells in the brain and spinal cord. They perform many functions, including biochemical control of endothelial cells that form the blood-brain barrier. A single astrocyte cell can interact with up to 2 million synapses simultaneously.

Hodgkin–Huxley model. The cell body of every neuron is enclosed by a plasma membrane consisting of bilayered lipid molecules. A lipid bilayer is a powerful electrical insulator, and in neurons, many of the protein structures embedded in the membrane are electrically active. An action potential (nerve impulse) travels down an axon, there is a change in electric polarity across the membrane of the axon (Fig. 3). In response to a signal from another neuron, sodium- (Na^+) and potassium- (K^+)–gated ion channels open and close as the membrane reaches its threshold potential. Na^+ channels open at the beginning of the action potential, and Na^+ moves into the axon, causing depolarization.

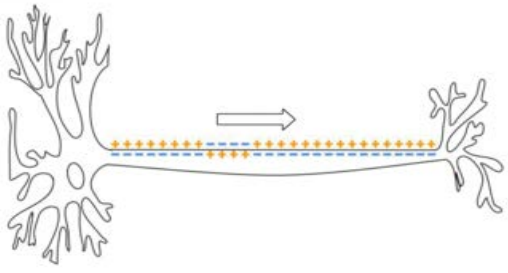

Fig. 3. An action potential (nerve impulse) travels down an axon changing in electric polarity across the axon membrane [6].

Repolarization occurs when K^+ channels open and K^+ moves out of the axon, creating a change in electric polarity between the outside of the cell and the inside.

Two English physiologists and biophysicists Alan Hodgkin (1914-1998) and Andrew Huxley (1917-2012) described the model in 1952 to explain the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon [6]. They received the 1963 Nobel Prize in Physiology or Medicine for this work.

The typical Hodgkin-Huxley model treats each component of an excitable cell as an electrical element (Fig. 4). The lipid bilayer is represented as a capacitance (C_m). Voltage-gated ion channels are defined by electrical conductances (g_n, where n is the specific ion channel) that depend on voltage and time. Leak channels are represented by linear conductances (g_L). The electrochemical gradients driving the flow of ions are represented by voltage sources (En) whose voltages are determined by the ratio of the intra- and extracellular concentrations of the ionic species of interest. Finally, ion pumps are represented by current sources (I_p). V_m denotes the membrane potential.

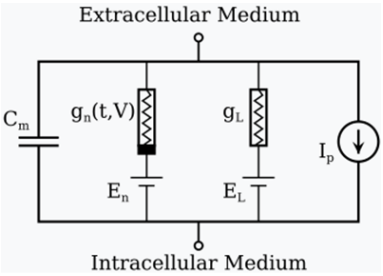

Fig. 4. Equivalent electrical circuit for the Hodgkin-Huxley model (a simplified version).

Mathematically, the current flowing through the lipid bilayer is written as

$$I_c = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t}$$

and the current through a given ion channel is the product of that channel's conductance and the driving potential for the specific ion

$$I_i = g_i(V_m - V_i)$$

Where V_i is the reversal potential of the specific ion channel, thus, for a cell with sodium (K) and potassium (Na) channels, the total current through the membrane is given by:

$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + g_K(V_m - V_K) + g_{Na}(V_m - V_{Na}) + g_l(V_m - V_l)$$

where I is the total membrane current per unit area, C_m is the membrane capacitance per unit area, g_K and g_{Na} are the potassium and sodium conductances per unit area, respectively, V_K and V_{Na} are the potassium and sodium reversal potentials, respectively, g_l and V_l are the leak conductance per unit area and leak reversal potential, respectively. The time-dependent elements of this equation are V_m, g_{Na}, and g_K, where the last two conductances depend explicitly on the membrane voltage (V_m) as well.

The actual version of the Hodgkin-Huxley model is described by a set of four nonlinear differential equations [7].

Synapse transmission. Synaptic transmission is the process at synapses by which a chemical signal (a

transmitter) is released from one neuron and diffuses to other neurons, generating a signal that excites, inhibits, or modulates cellular activity. All synapses generally use the same basic mechanism to release a transmitter and activate the target cell. When an action potential arrives at a synaptic ending, it causes the release of a neurotransmitter stored inside synaptic vesicles. Three ions and their concentration gradients are of particular importance: sodium (Na+), potassium (K+), and calcium (Ca2+). When the neuron is at rest, Na+ is more concentrated on the outside than the inside, K+ is more placed on the inside, and Ca2+ is much more placed on the outside. Action potentials open voltage-sensitive calcium channels in excitable cells, leading to an influx of calcium ions (Fig. 5).

The transmitter diffuses to the target cell, where it binds to a receptor protein on the external surface of the cell membrane.

The presynaptic terminal is at the end of an axon and is the place where the electrical signal (the action potential) is converted into a chemical signal (neurotransmitter release). The postsynaptic terminal membrane is less than 50 nanometers away and contains specialized receptors. The neurotransmitter rapidly (in microseconds) diffuses across the synaptic cleft and binds to specific receptors.

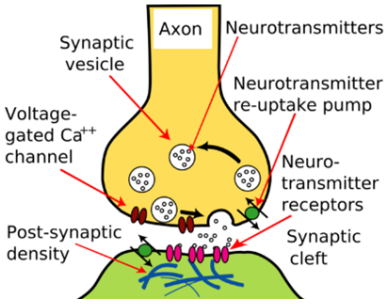

Fig. 5. Synapse transmission: calcium control of neurotransmitter release

III. Energy for the Brain

The brain consumes around 20-25% of the body's glucose, despite only representing 2% of its weight. How does the energy in our brain distribute? The energetic demands for synaptic transmission are estimated at 50 %, 10-15 % for action potentials, and 9-18 % for other signaling-related processes, including calcium responses and glutamate/GABA recycling in neurons. Glutamate is the most abundant excitatory neurotransmitter in the nervous system.

Glucose is the most important fuel for the brain to fulfill complex neurological functions including neuronal signal transmission, and nonsignaling activities (axonal transport, resting potential, etc.). Additionally, glucose metabolism provides also the carbon to synthesize nucleic acids, fatty acids, and amino acids (used by the brain as alternative fuels).

The main energy unit of our brain cells is a molecule called adenosine triphosphate (ATP), which our body makes from sugar and oxygen. In glycolysis, glucose and glycerol are metabolized to pyruvate (in the highly sophisticated path called Krebs Cycle). As a result, each glucose molecule produces about 30 equivalents of ATP. Therefore, glucose metabolites support ATP production. An average human adult processes around 50 kilograms of ATP daily. ATF fulfills complex neurological functions (Fig. 6).

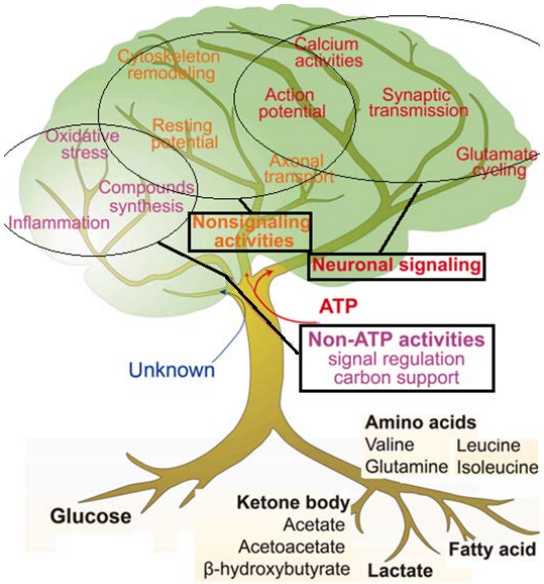

Fig. 6. Energetic fuels supporting the ATP-dependent and ATP-independent actions in the brain [8]

Vitamin C is an antioxidant. To understand the role of vitamin C one looks at the picture of vitamin concentrations in our body. The highest concentrations of vitamin C are found in the brain and neuroendocrine tissues especially the adrenal gland, which may range from 1 mM to 3 mM. These concentrations are 15–50 times higher than those in the plasma, pointing to the existence of active transporting mechanisms (Fig. 7).

Human red blood cells (RBCs) express a high number of glucose transporters (GLUT) but have no sodium-dependent vitamin C transporters, and the intracellular concentration of vitamin C in these cells is similar to that in the plasma. The concentration of vitamin C in the cerebrospinal fluid is ~5–10 times higher than the plasma. A larger arrow indicates the main direction of vitamin C transportation.

Glucose metabolism is involved in oxidative stress modulation (as an important feature). It is the source of reactive oxygen species (ROS): e.g. hydroxyl radical; hydroxide ion; hydrogen peroxide, nitric oxide. Ascorbic acid (vitamin C), an essential nutrient with well-known antioxidant potential, protects the brain from oxidative damage in various models of neurodegeneration (Fig. 8).

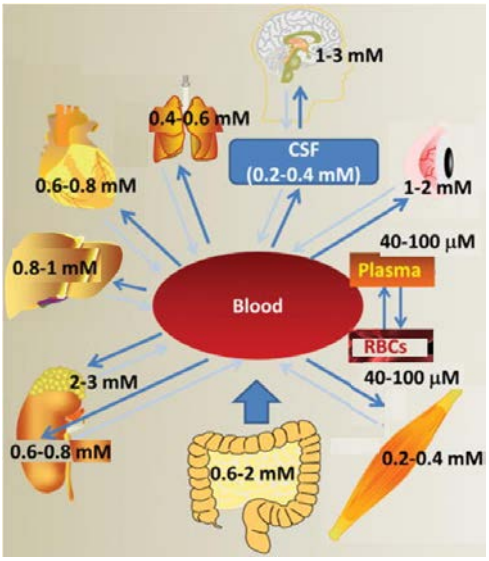

Fig. 7. Tissue levels of vitamin C

Vitamin C accumulates in mitochondria, where most free radicals are produced. Ascorbic acid protects the mitochondrial genome and membrane.

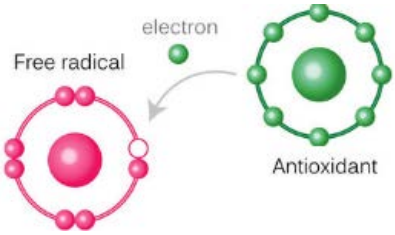

Fig. 8. How do antioxidants work?

Note that the chemistry of ascorbic acid underlying its antioxidant properties is a bit more complex (Fig. 9). Vitamin C can sequentially donate two electrons and donate electrons to reactive free radicals, which then become reduced. The loss of one electron results in vitamin C being oxidized to the ascorbate free radical, it, in its order, can be reduced to vitamin C by gaining one electron or further oxidized to dehydroascorbic acid (DHA) by losing another electron. DHA is stable for a few minutes and can be reduced to AA [10].

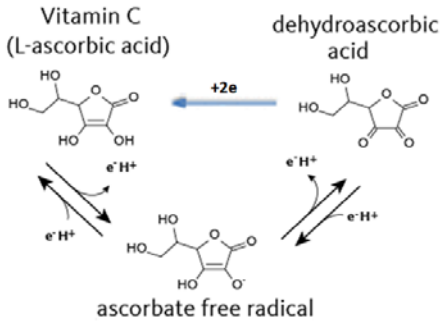

Fig. 9. Vitamin C (L-ascorbic acid, AA) is an electron donor [9].

Related to this oxidation-reduction (redox) potential, even in small amounts, vitamin C can protect indispensable molecules in the body, such as proteins, lipids (fats), carbohydrates, and nucleic acids (DNA and RNA), from damage by free radicals and reactive oxygen species (ROS) that are generated during normal metabolism (Fig. 10).

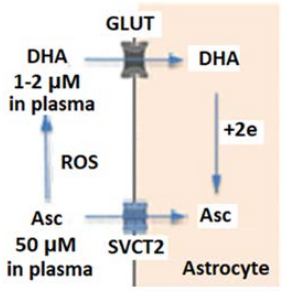

Fig. 10. A simple view of cellular metabolism of vitamin C. Cellular uptake of reduced (ascorbate, Asc) and oxidized (dehydroascorbic acid, DHA) forms of vitamin C. Extracellular concentrations of DHA and, consequently, the importance of its uptake is higher for cells that release large amounts of oxidants during the inflammatory responses [11].

IV. Vitamin C and Neurodegenerative Diseases: A Simple Model

The situation with tripartite synapse modeling is becoming even more complicated as deeper molecular biology studies are going on. However, one can hope that even this modest amount of knowledge about the brain's work will allow the creation of new models of neurodegenerative diseases.

How does vitamin C penetrate a neuron? This question is discussed everywhere (e.g. [12-13]). The mechanisms for DHA and Asc entering the CSF are different. For DHA to enter the CSF, it must be taken up by the endothelial cells in the blood-brain barrier (BBB). Then, it may pass into the CSF through the GLUT 1/3 receptors. Asc's journey begins by being taken up by the epithelium of the choroid plexus. It then may enter the CSF by passing through the SVCT2 receptors on the apical membrane of the choroid plexus [13].

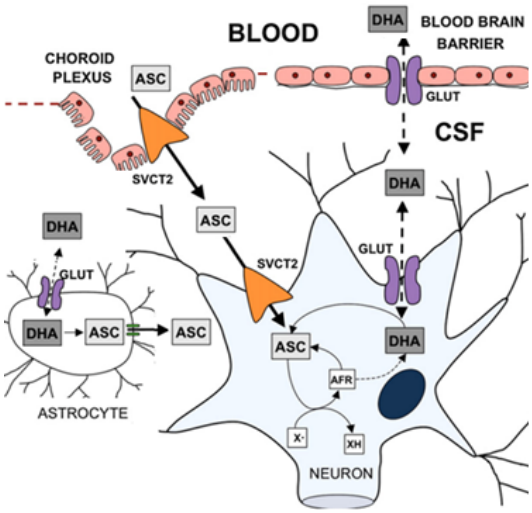

Fig. 11. Transport of ASC and DHA through the Brain [13]. Notations: AFR, ascorbate free radical; X·, oxidizing free radical species.

The DHA, which is now in the extracellular space, may then be recycled into Asc for the neurons to use with astrocytes, types of glial cells. However, only GLUT 1 receptors exist on the astrocyte cells, so DHA uptake is significantly slower. Then, DHA is reduced to Asc inside the astrocyte, before the Asc is released back into the extracellular space through glutamate-induced cell swelling. This "recycled" Asc can then be used again by the neurons. Evidence has been provided that, during synaptic activity, there is increased SVCT2 expression on the neuron. The

biochemical flow chart in Fig. 11 from [13] concisely captures the above descriptions.

The author [12] proposes a mathematical model that captures the biochemical dynamics between AA, dehydroascorbic acid (DHA), and ROS in the brain and performs simulations under control and neurodegenerative disease situations.

Bukkuri's paper [12] starts with the illustration of dehydroascorbic acid (DHA) and ascorbate (Asc) uptake into the central nervous system (CNS). It occurs in two steps. First, they must be transported from the plasma into the cerebrospinal fluid (CSF), and then from the CSF into the neuron.

Tripartite synapse mathematical model. From the above biochemical framework, the following mathematical model of 9 differential equations was constructed [12]:

$$\frac{dA_p}{dt} = pA_p(1-\frac{A_p}{\kappa}) - cA_p(1-\frac{A_c}{\mathcal{L}}) - d_A A_p \quad (1)$$

$$\frac{dD_p}{dt} = bD_p(1-\frac{D_p}{\xi}) - eD_p(1-\frac{D_c}{\chi}) - d_D D_p \quad (2)$$

$$\frac{dA_c}{dt} = (1-\frac{A_c}{\mathcal{L}})(cA_p + sA_a) - \alpha f A_c(1-\frac{A_n}{\upsilon}) - d_A A_c \quad (3)$$

$$\frac{dD_c}{dt} = (1-\frac{D_c}{\chi})(eD_p + gD_n + zD_a) - hD_c(1-\frac{D_n}{\omega}) - iD_c(1-\frac{D_a}{\psi}) - d_D D_c \quad (4)$$

$$\frac{dA_n}{dt} = (1-\frac{A_n}{\upsilon})(\alpha f A_c + jD_n) - \alpha k A_n(1-\frac{D_n}{\omega}) - d_A A_n \quad (5)$$

$$\frac{dD_n}{dt} = (1-\frac{D_n}{\omega})(hD_c + \alpha k A_n) - jD_n(1-\frac{A_n}{\upsilon}) - gD_n(1-\frac{D_c}{\chi}) - d_D D_n \quad (6)$$

$$\frac{dR_n}{dt} = \alpha(q - R_n A_n r k(1-\frac{D_n}{\omega})) - d_R R_n \quad (7)$$

$$\frac{dA_a}{dt} = (1-\frac{A_a}{\tau})mD_a - sA_a(1-\frac{A_c}{\mathcal{L}}) - d_A A_a \quad (8)$$

$$\frac{dD_a}{dt} = (1-\frac{D_a}{\psi})iD_c - mD_a(1-\frac{A_a}{\tau}) - zD_a(1-\frac{D_c}{\chi}) - d_D D_a \quad (9)$$

Here, A_p and D_p in equations (1) and (2) represent the AA in the plasma (choroid plexus) and DHA in the plasma (blood-brain barrier). A_c and D_c are the AA and DHA in the CSF (eq-s 3 and 4). A_n, D_n, and R_n are the neuron's AA, DHA, and ROS (eq-s 5-7). A_a and D_a are the AA and DHA in the astrocyte (eq-s 8 and 9).

Note that the results shown in Fig. 12 are following physiological results. Due to the degradation of AA and DHA in the brain, one can see the ROS production slowly increase at the end of the time, when all the AA and DHA concentrations are nearing 0. Moreover, one can see that the DHA and AA in the plasma almost immediately drop to 0 as their AA and DHA are transported to the CSF. Then, one can see that the AA and DHA in the CSF decrease faster next, and the AA and DHA in the neurons decay slowly. This is under the normal physiological observations, which show the most AA concentrated in the neuron, then in the CSF, and lastly in the plasma surrounding the brain.

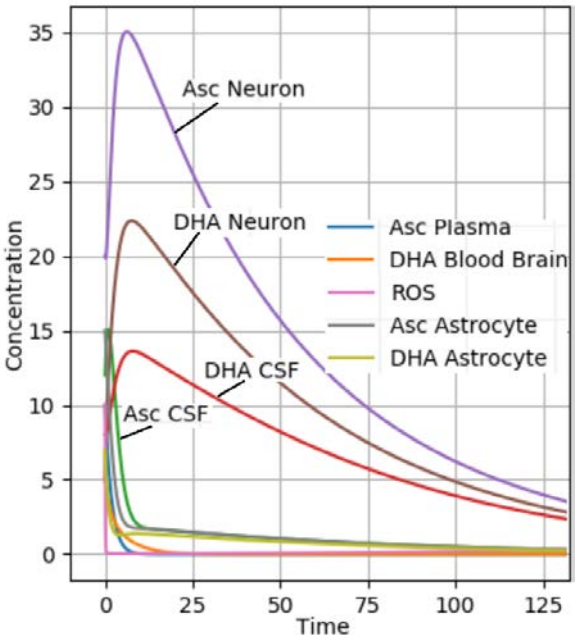

Fig. 12. Dynamics of AA, DHA, and ROS in a Control Case [12]

As an example of a neurological disorder from [12], we show Alzheimer's Disease (AD) case (Fig. 13). It has been noted that AD patients have low plasma and CSF ascorbate levels, despite adequate nutritional intake. Neuropathological change that occurs with AD onset is the presence of Aβ-plaques that accumulate in the cytosol. Studies have shown that Aβ aggregation promotes ROS production.

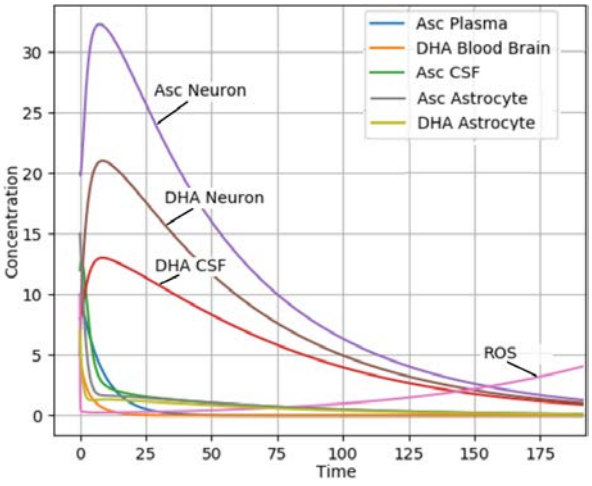

Fig. 13. Dynamics of AA, DHA, and ROS in AD [12]

As expected, we see greatly increased ROS production. This cannot be solved with a few AA intakes. It must be dealt with consistently since AD modifies the actual parameters of the system.

In [12], several neurodegenerative diseases such as Huntington's Disease (HD), and ischemic strokes all show signs of excess oxidative stress due to increased production of reactive oxygen species (ROS).

In our opinion, the essence of neurodegenerative diseases is much more complicated, particularly due to dependence on the digestive system (so-called leaky gut problem discussed below).

V. MODELING ON CALCIUM WAVES

Calcium control of neurotransmitter release. As mentioned above, in 1952 A. Hodgkin and A. Huxley explained the ionic (Na+ and K+) mechanisms underlying the initiation and propagation of action potentials in the squid giant axon. In 1967, it was also identified that Ca2+ has an essential role for neurotransmitter release [16], it became clear that calcium ion entry through membranes was key to many important processes in nerves.

Synaptic transmission is initiated when an action potential invades a nerve terminal, opening Ca^{2+} channels [17], which gate a highly localized, transient increase in intracellular Ca^{2+} at the active zone. Ca^{2+} triggers synaptic vesicle exocytosis, thereby releasing the neurotransmitters contained in the vesicles and initiating synaptic transmission (Fig. 14).

Neurotransmitters are chemical messengers passed from one neuron to another neuron. In total, there are about 500 neurotransmitters. The two most common (90%+) neurotransmitters in the brain, glutamate and GABA, have largely consistent actions. When an action potential reaches the axon terminal, it opens voltage-gated calcium channels, allowing calcium ions to enter the terminal. Calcium causes synaptic vesicles filled with neurotransmitter molecules to fuse with the membrane, releasing their contents into the synaptic cleft. The neurotransmitters diffuse across the synaptic cleft and activate receptors on the postsynaptic neuron. High cytosolic calcium in the axon terminal triggers mitochondrial calcium uptake, which, in turn, activates mitochondrial energy metabolism to produce ATP and support continuous neurotransmission.

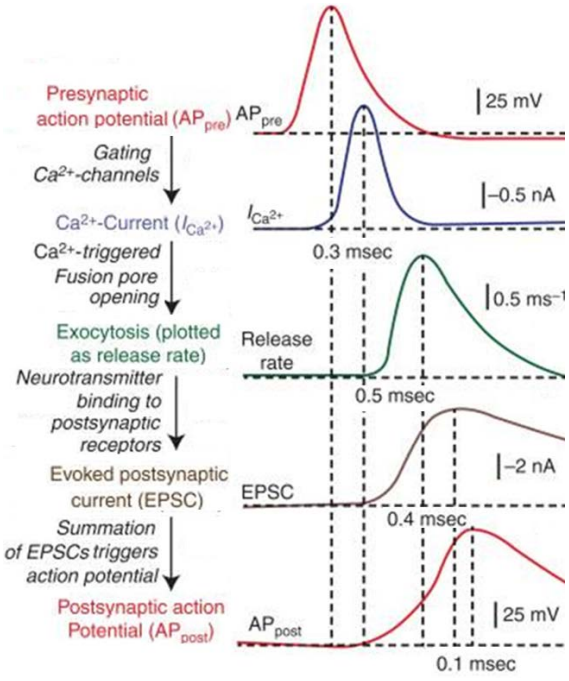

Fig. 14. The sequence and time course of synaptic transmission [17]. Note that Ca^{2+} currents and EPSC are shown inverted.

Three calcium wave models. Research since the mid-1990s has shown that astrocytes propagate intercellular Ca^{2+} waves over long distances in response to stimulation, and, similar to neurons, release gliotransmitters in a Ca^{2+}-dependent manner. Calcium waves could synchronize neuron activity (not yet well understood).

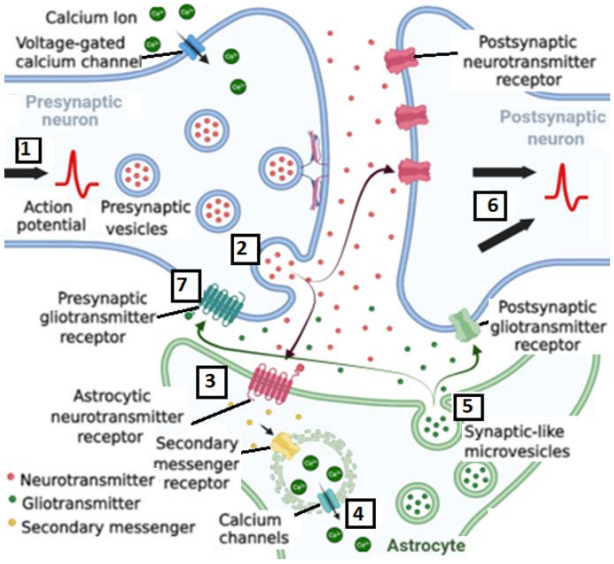

Fig. 15. The interplay between astrocyte, presynaptic, and postsynaptic neurons in the tripartite synapse [15].

First model. Fig. 15 shows the interplay in the tripartite synapse between astrocyte, and presynaptic and postsynaptic neurons [18]. There are the following seven steps:

1) Arrival of the action potential,

2) Neurotransmitter release,

3) Production of a secondary messenger,

4) Ca2+ exchange between the endoplasmic reticulum (ER) store and the cytoplasm of the astrocyte,

5) Release of glial mediators (Gm) or gliotransmitters,

6) Generation of action potential in the postsynaptic neuron due to currents induced by the synapse and the astrocyte,

7) Modulation of the neuronal activity of the presynaptic neuron due to gliotransmitters.

Based on this knowledge mathematical models were built [15]. These can be employed to simulate astrocytic networks integrated with synaptically bound neurons, offering insights into the functional role of Ca2+ waves in regulating synaptic transmission and allowing investigation of pertinent nonlinear mechanisms.

The α, β, γ_i, γ_j, and δ (Fig. 16) are the main parameters responsible for the activation and influence of astrocytes. The proposed tripartite synapse mathematical model contains 16 equations.

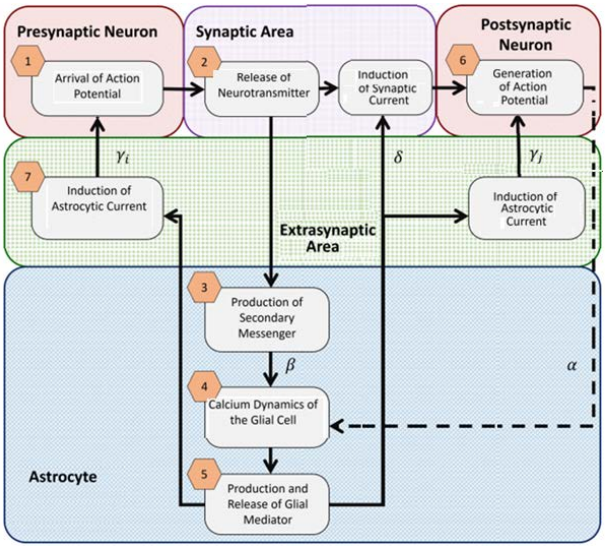

Fig. 16. The functional diagram of the proposed tripartite synapse model [18]

Second model. The release of intracellular calcium ions in the astrocyte is modulated by several mechanisms occurring in the cell. The more complex tripartite synapse mathematical model [19] contains 22 ordinary differential equations describing glutamate dynamics in the synaptic cleft.

Third model. In [20], the IP3-dependent release of Ca2+ from internal calcium stored is considered, and 20 equations describe the astrocyte-neuron communication.

The influence of astrocytes on neuronal communities via calcium waves has become especially relevant. However, it is currently unclear whether these neuron-astrocyte interactions can lead to the synchronization of neurons or, at least, neuron spillover [21].

VI. What is the role of vitamin C in calcium channel regulation?

The original goal - the influence of vitamin C - remains unclear since it undoubtedly affects the distribution of calcium. In other words, the study of the tripartite synapse, uncovering the brain's secrets is a vast field of research.

Calcium ions and a transient rise in their concentration are crucial for all neuronal processes. Extracellular Ca2+ influx (through specific ion channels) or Ca2+ release from intracellular stores (endoplasmic reticulum, mitochondria) are precisely controlled. Ca2+ regulates the functioning of the CNS.

It is generally well-accepted that neurotransmitter release is a Ca2+-dependent event. In its order, neurotransmitters can regulate the release and uptake of vitamin C. That bi-directional communication between these processes allows for fine-tuning of the homeostatic response to environmental stimuli.

Several groups of calcium channels are responsible for the influx of Ca2+ into the cells. They differ in structure, localization, and functional properties [22] and regulation by vitamin C (Fig. 17). The four major channel categories include:

1. Voltage-gated calcium channels (VGCCs) comprise high, intermediate, and low voltage-activated channels that are important mediators of depolarization-evoked release of neurotransmitters. Low-voltage-activated Ca2+ channels have been identified as a direct target for vitamin C action.

2. One of the most active groups of receptors that transmit glutamate signaling in the brain is the family of ionotropic NMDA receptors (NMDARs). They form cation-permeable channels that mainly transport Ca2+ but also Na+ and K+.

3. Transient receptor potential (TRP) channels are another group of calcium channels. TRP channels are evolutionarily conserved integral membrane proteins. The TRP channel superfamily is a heterogenous group of more than 28 representatives that regulate Ca2+ influx acting as biosensors and transducers [23]. They are present in the cellular membranes and can be activated by numerous physical and/or chemical signals. Due to their diversity in activation, mechanisms, and selectivity, TRP channels can be considered multiple signal integrators.

4. Receptor-operated calcium channels (ROCCs) are metabotropic cation channels that, following stimulation of GPCRs, initiate a cascade of pathways via G proteins and contribute to phospholipase C-dependent Ca2+ entry.

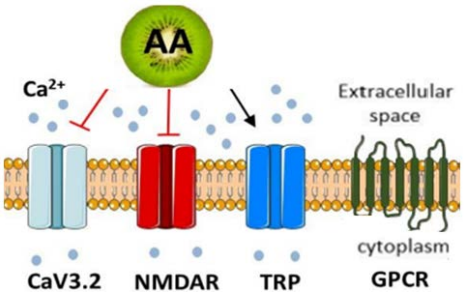

Fig. 17. The regulation of Ca2+-permeable channels by vitamin C [19]. Notations: CaV3.2—T-type voltage-dependent Ca2+ channel; NMDAR—N-methyl-D-aspartate receptor; TRP—transient receptor potential channel; GPCR—G-protein-coupled receptor; AA—ascorbic acid (vitamin C). Red arrow—inhibition; black arrow—activation.

The coupling between calcium and vitamin C points to a functional impact from the activities of both compounds in the brain (several different molecular mechanisms have been identified as well). Two main factors determine vitamin C's antioxidative properties: (1) the availability of its reduced form—ascorbate and (2) the possibility of dehydroascorbate (oxidized form) re-oxidation.

Equally important is a specific mechanism of transport that concentrates vitamin C intracellularly, thereby enhancing its function as an enzyme and antioxidant. Vitamin C has been demonstrated to regulate neurotransmitters, receptors, and ion channels, and all these activities are directly or indirectly linked with calcium. The main physiological role of vitamin C is the inhibition of

redox imbalance produced by the stimulation of glutamate receptors and a subsequent increase in intracellular Ca2+. Interestingly, vitamin C release can be promoted by glutamate in a receptor-dependent manner; thus, glutamate induces an important protective mechanism by regulating the release of this antioxidant.

Thus, under physiological conditions, including properly controlled calcium homeostasis, vitamin C should have an active role in the maintenance of neuronal function, actively protecting the brain from abnormal excitability. The apparent complexity of vitamin C mechanisms engaged in neuronal regulation clearly indicates its important role, but a number of questions remain open.

Vitamin C does not act solely and coexisting factors and/or compounds, yet undefined, can alter ultimate cell response. Further work examining these potential relationships will greatly enhance our understanding of vitamin C's role in brain function. Moreover, recognition and precise characterization of neurotoxic molecular events observed in neurodegenerative disorders may facilitate the identification of novel therapeutic targets for vitamin C.

VII. Conclusion: Neurogastroenterology is Born

The review [24] updates the current state of knowledge of the role of vitamin C on neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, and amyotrophic sclerosis, as well as psychiatric disorders including depression, anxiety, and schizophrenia (Fig. 18). The attention is attributed to the mechanisms underlying possible therapeutic properties of ascorbic acid in the presented disorders. Consumption of vitamin C is related to nutrition. Because humans are unable to synthesize vitamin C, it is an essential dietary component.

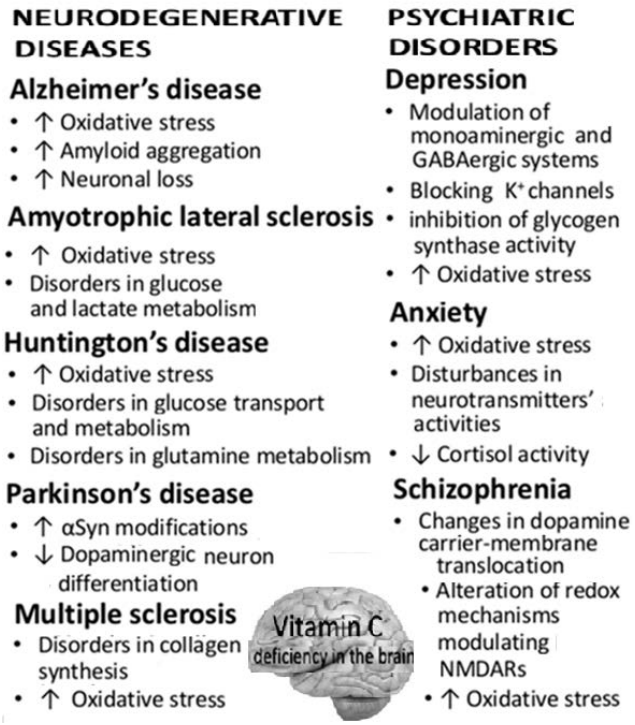

Fig. 18. The main potential consequences of vitamin C deficiency and the pathogenesis of neurological disorders [24]

"Leaky gut" is the name given to increased intestinal permeability, a generally recognized condition in which the spaces between the cells of the intestinal lining increase. Disruption of the healthy flora (dysbiosis) has been implicated as a driver for a wide range of neurodegenerative diseases (Fig. 19).

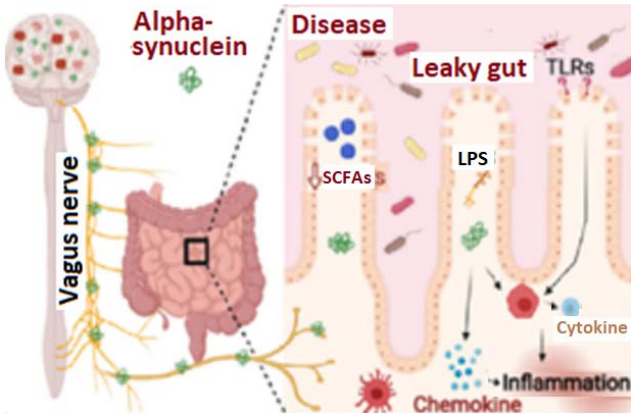

Fig. 19. The transition from a healthy gut to dysbiosis has been associated with neurodegenerative diseases. Bacterial components can permeate through the intestinal wall to activate resident intestinal immune cells, which generate chemokines and cytokines that induce inflammation. Based on preclinical evidence, it is hypothesized that the transneuronal migration of pathological proteins, such as alpha-synuclein, could occur from the gut to the brain via the vagus nerve [25]

Let's comment on Fig. 19. *On the positive side*, short-chain fatty acids (SCFAs) are primarily produced by the fermentation of dietary fiber in the gut microbiome. Derived from intestinal microbial fermentation of indigestible foods, SCFAs in the human gut are acetic, propionic, and butyric acids. They are the main energy source of enterocytes, making them crucial to gastrointestinal health. Toll-like receptors (TLRs) are found in various layers of the intestinal epithelium. They can recognize bacteria and are involved in establishing homeostasis in the intestine. *On the negative side*, lipopolysaccharides (LPS) are bacterial toxins that can cause health problems if they enter the bloodstream. LPS is usually found safely in the intestines but can enter the bloodstream if you have an infection, leaky gut, or eat many fatty foods.

As scientists suggest nowadays, Parkinson's disease (PD) begins with bidirectional communication between the microbiota and the immune system, thus there is an exciting possibility that progression could be stopped before it reaches the brain [26, 29].

The clinical and pathological findings support the hypothesis that aSyn disease in PD occurs via a gut-brain pathway. For early diagnosis and early management, it is of utmost importance to identify pathogenic aSyn in the digestive system, for example, by gastrointestinal tract biopsies (Fig. 20).

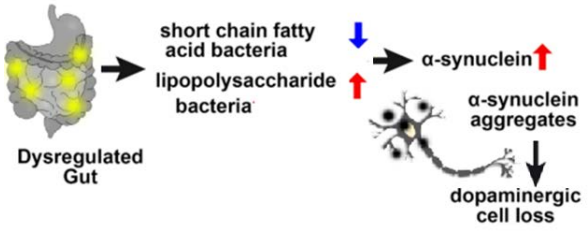

Fig. 20. Microbiological explanation of PD [27]. Before dopaminergic depletion in the brain and even before the manifestation of PD symptoms, preclinical and clinical evidence indicates a dysregulated gut characterized by downregulated short-chain fatty acid bacteria but upregulated lipopolysaccharide bacteria, resulting in abnormal accumulation of α-synuclein in the gut that subsequently aggregates in the brain and causes dopaminergic degeneration.

AD entails a complex neurodegenerative process that involves the formation of amyloid-β (Aβ) plaques. AD patients suffer from neuronal loss. The pathogenesis of AD coincides with dysfunctional intestinal microbiota (Fig. 21). The bacteria that invade the intestinal microbiome can excrete huge amounts of amyloids and lipopolysaccharides, contributing to AD pathology.

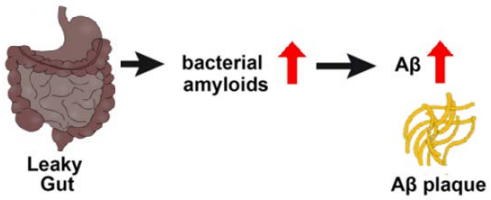

Fig. 21. A leaky gut may allow the transport of bacterial amyloids from the intestines to the brain, where aberrant aggregation of amyloid β (Aβ) occurs, forming Aβ plaques implicated in AD pathology and symptoms [27]

Disorders of gut-brain interaction, previously referred to as functional gastrointestinal disorders, affect 40.3% of adults in the general population and are diagnosed in 34.9% of new adult referrals to secondary care gastroenterology services [28]. Despite their high prevalence, studies published by investigators based in Germany, the UK, and the USA demonstrate a mismatch between the clinical burden of DGBI and their representation in medical school and postgraduate curricula.

In summary, nowadays dysbiosis has been implicated as a driver for a wide range of neurodegenerative diseases and psychiatric disorders, thus a new science – neuro-gastroenterology – is born. One old prediction comes true: “The main refuge of madness is the stomach and intestines”. This is a sentence said by the “father” of modern psychiatry, French psychiatrist Philippe Pinel (1745-1828), back in 1807 (that is, more than 200 years ago). A significant contribution to the new science can be considered Linus Pauling’s hypothesis: mega doses of vitamin C can prevent and treat many diseases, including cancer.

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AUTHOR

Manfred Sneps-Sneppe (born May 24, 1935, Rezekne, Latvia) – Doctor of Technical Sciences, Professor, Emeritus Scientist of the Latvian Academy of Sciences (since 2021). Graduated from the University of Latvia in mathematics in 1959. 1962-1965 postgraduate study at Moscow State University (Department of Probability Theory and Mathematical Statistics). In 1965 he defended his PhD dissertation on mathematical methods in medicine, in 1969 – doctoral dissertation on telephone exchange calculations, and in 1982 he was awarded the title of professor. He worked at the All-Russian Research Institute of Medical Instrumentation (1965-1978), the Central Research Institute of Communications (1978-1984), the Riga Research Institute of VEF (1984-1989), as a professor at the University of Latvia (1989-1992), and as head of the Department of Telecommunications at Riga Technical University (1992-1995). Nine postgraduate students defended their dissertations in medical engineering, and 12 doctoral students defended their dissertations in telecommunications.