ON BIOLOGICAL ACTIVITY OF SELENIUM COMPOUNDS

(Ideas of G.M. Abdulayev in modern perceptions about biological role of Se).

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The inorganic compounds (sodium selenide) and organic compounds (Ebselen) can significantly influence on the development of virus infection including COVID-19. The oxidative stress is the one of COVID-19 key damaging elements. One of the main reasons of its activity is that M-RNA COVID-19 has the gens of important seleno-containing proteins (GP, TRx, SelenP) for synthesis and expression of which use the internal resources of selenium, forming its deficit that leads to limit of selenoprotein synthesis of organism. That's why selenium status can have the significant value for both processes of infection beginning and severity of disease carrying out and following complications connected with damage of immune response and development of oxidative stress.

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INTRODUCTION

In the history of selenium research, since its discovery by I.Berzelius in 1817, one can distinguish some separate stages associated with investigation of its activity and distribution in nature, in particular, in cells of living organism [1,2]. First of all, these are works of American scientist K.Shwatrz who established the anti-necrotic role of Se in organisms of several animals in 1957 [3] and thus, he proved the illegality of attitude to this element only as purely toxic [4, 5].

The information that known antiperoxide enzyme glutathione peroxidase [6] protective towards hemoglobin, is the seleno-dependent protein having the wide antioxidant properties was given in 1973 in works of L.A. Floe and I.H. Rotruk [7,8]. The works of Azerbaijan scientist G.M.Abdullayev, whose activity stimulated the complex study of selenium biological properties in Azerbaijan scientific centers on physics and biology, play important role in development of this stage of investigation. The facts of light sensitivity amplification of organ of sight by selenium (sodium selenite), stability of tissues and cells to oxidative stress and also stability of whole organism to such disturbing factor of environment as radioactive radiation and mutagenesis caused by it and others, were established. The big cycle of works is devoted to the influence of selenium on growth and multiplication of vegetable objects and micro-organisms, selenium metabolism in organs and tissues of oncological sicks, deceleration mechanism by selenium of tumor cell growth on inhibition model of activities of DNA and RNA polymerases. The cycles of works are made on the example of the flu virus and the effectiveness of sodium selenite on inhibition of replicative and transcription processes associated with genetic material of flu virus A (H_3N_2). Note that Azerbaijan chemists synthesized the series of effective selenium organic compounds in 70-80th which showed the high biological properties against series of pathologies. Comparing the structural formulae of these compounds with those which nowadays are used in clinic medicine and agriculture (veterinary) (Ebselen, selenpiran and others) we accept that choice of synthesis of effective selenium organic compounds is right.

In 70-80th it was shown that Se localizes in all cells of organism [9,10] and mortality from cancer depends on regional soil supply by Se [5,11,12]. Selenium deficit increased the virulence of low-activity virus Koksaki-B3 damaging the heart muscle so-called Keshan disease by Chinese province suffering from selenium deep deficit [13,14]. The three selenium-containing enzymes on different levels taking part in regulation of iodine exchange were identified in 90th [15]. These discoveries stimulated big interest to its intracellular regulation functions. Nowadays, more than 25 of selenium-containing proteins in the cells of most different organs and tissues have been identified. It is established that the part of the selenoproteins has the concrete physiological functions, moreover, that many of them have anti-oxidative functions [15,16]. The unique mechanism of selenoprotein synthesis so-called SESIS-mechanism had been also discovered. It includes 21 required amino-acid selenocysteine which is coded by stop-codon UGA in structure m-RNA. Selenium is included in selenoproteins through selenocysteine t-RNA which is synthesized by the means of transition of Se group in serine t-RNA from selenium-phosphate. This mechanism is unique because it has co-translation character at which the protein synthesis on ribosomes takes place simultaneously with synthesis of 21st amino-acid (i.e. transformation of serine in selenocysteine) [16,17].

In the end of 90th and early 2000th there was the supposition that Se has the anticancer activity along with antivirus one [13,18]. Earlier known fact of Koksaki-B3 inhibition virus activity is the reason of it [18]. Recently, it had been revealed that such virus diseases as Khant fever [19], Zika [20], hepatitis C[21], HIV [22-24], Ebola [25-27], different flus [28-30] take places difficultly at selenium deficit which along with Zn and vitamin D plays the important role in supply of normal immunity [31,32]. The mortality

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from HIV in selenium-deficit regions was in 3-5 times higher than in normal ones. For HIV infection the mortality in several regions of Africa achieved 20-multiple exceed [22,23]. Taking under consideration that genome COVID-19 contains the elements of HIV, Ebola, SARS-CoV-1 and etc. [24-26, 33, 34, 35] on the base of analysis of the present publications, collaborators of Institute of Biophysics of ANAS made an assumption that increasing selenium deficit in many countries is caused by significant decrease of ecological situation [35]. In particular, the increasing atmosphere gas contamination leading to soil oxidation, heavy metals and chemicalization of agriculture lead to strong decrease of selenium slip forms, i.e. to depletion of plants by selenium and correspondingly, to weakening of supply of animals and plants by selenium [35]. Note that last 40-50 years the thinning-down of atmosphere ozone layer and consequently, increase of hard component of sun UV radiation stimulating the photo-oxidative processes required the compensation and increased discharge of anti-oxidants including Se has been taken place. We can add that general climate warming including so-called greenhouse effect can lead to increase of selenium deficit and correspondingly, to appearing of earlier “sleeping” virus types or increase of virulence of already present ones [35a].

Nowadays, considering the Se participation in many biological processes including the development of virus infections, it is necessary to accept that predictions of G.M.Abdullayev on role of this element in life processes and activity of biological objects in many aspects were prophetic ones.

The widely spread dangerous virus diseases, that have appeared recently, are caused, as a rule, by RNA-viruses containing selenoproteins in their genome (glutathione peroxidase, tioredoxinreductase, SeP and others). The attempt to generalize previously available facts and information on Se participation in development processes of these virus infections is the aim of the present investigation. This is important for both understanding of Se role and generation of optimal method use of seleno-containing compounds for medical treatment of virus diseases.

COVID-19 (SARS-COV-2)

Not considering details of SARS-CoV-2 appear, one can make some static analysis of factors influencing on its distribution, virulence, pathogenicity of ecological factors taking under consideration the clear irregularity of its consequences on people health in different countries, having the different both social-economical and geographical conditions. Here we note the analogy with earlier known virus diseases connected with disturbance of immune response, in particular, we note HIV infection [25,26] the genome of which is the part of present COVID-19 genome [33, 34].

Note, that we earlier noted that HIV infection distribution is geographically connected with regions of Se low content in soils. In Africa HIV infection has become the pandemic character and quarter of population suffers from this disease. In particular, in Zambia, Botswana and Zimbabwe the quantity of infected people is 20-25% [35]. Besides, Senegal in West Africa has the lowest indexes of distribution of AIDS and cancer along with highest soil levels enriched by Se [36].

The connection between increased mortality from AIDA and selenium ecological deficit is shown for US [35]. It was shown that the increased mortality from AIDS is observed at selenium lowered level. The investigations carried out by Etan U.Taylor and his collaborators also proved that AIDS, Kaposi's sarcoma and cancer diseases are more spread in regions with seleno-deficit soils and this is true for not only for Africa, but for whole World [34]. In China seleno-deficit regions are known as “Chinese disease belt”. Here, the everyday average selenium consumption is less than 10 μg (norm is 100 μg) that leads to activation of Koksaki B3 virus mutation leading to heart pathological state in regions of ”Chinese disease belt”. The increase of selenium content in food ration can also significantly decrease the sphere of cancer activity and decrease of mortality from cardiac infarction [13,14].

In Europe, Russia and Ukraine the monitoring investigations which have revealed the seleno -deficit of population, are carried out. The legislative measures on enrichment of food ration by selenium have been accepted in several states. It is mentioned that last 20-30 years the supply of selenium with food has decreased in 50% even in such conservative and healthy country as Great Britain. We don’t mention the countries of “third world” where very bad situation with food. The wide use of import products of “intensive agriculture production” (this is actual for Azerbaijan population) is included in number of factors defining the selenium content in organisms [35, 37, 38]. Note that genome of many RNA viruses contains the code for seleno-dependent glutathione-peroxidase (GP). Some changes in environment that have appeared in the end of 20^{th} to beginning 21^{th} hundred have significantly improved AIDS competitive ability that became the reason of AIDS wide spread. These changes were analyzed in the works of Taylor and his colleagues [25, 25, 34]. These authors also showed that in the middle of 90^{th} there was virus group having the gen coding the seleno-dependent glutathione peroxidase. This virus group included HIV-1 and HIV-2, also virus Koksaki B3 defining the development of cardiomyopathy (cardiac infarction) and viruses of B and C hepatitis’s and others. The authors supposed that this fact is connected either with Se role as oxidant minimizing the consequences of oxidation stress or with its influence on gen activity in the response on HIV infection [35].

In 2014 – 2016 Taylor and his collaborators, carried out detail comparative investigations of Ebola and HIV-1 genomes showed that in their genomes towards with glutathione peroxidase the specific weight of another seleno-containing enzyme thioredoxinreductase (TRx) the gens of which overlap each other. Thioredoxinreductase has big oxidation-

recombination influence on replicative processes that causes extremely depletion of organism by Se at development of this diseases [34].

According to COVID-19 we can mention that secondary respiratory symptoms are considered more dangerous ones than the primary ones, i.e. COVID-19 is rather vascular disease than respirator one [33, 34, 40, 41]. The injury of heart and vascular system is the main reason of mortality. It is seemed that more than 50% mortality causes by myocardium disturbance (main activation symptom of Koksaki B3) and system global blood coagulability leading to hypoxia or asphyxia [41]. On the base of analysis of present publications one can conclude that patients with normal selenium level in blood and glutathione peroxidase, revealed in period of previous pandemia of H1N1 flu, significantly easier treat this disease [33, 34]. On model tests (on mice) the analogous results had been obtained, i.e. mice which were given selenium died in 3 times [33,34]. The analogous results were obtained for flu virus A (H_3N_2) [34]. In last epidemiological investigations connected with COVID-19 carried out in China by international group of scientists were shown the presence correlative connection between selenium content in hair and recovering: survival rate in 5 times (Hubai province, center Uhan) in comparison with lowered selenium status (Heylunczan province). Moreover, the weakening of development form of disease itself is the important index. This is seen even on the example of one Chinese province (Uhan) but in different cities with different selenium status where mortality ratio is 1:3 [42].

In order to answer to question how Se can influence of virus infection, in particular, on COVID-19 and other similar RNA virus infections, it is necessary to pay attention on following circumstances. The virus particle consists of hydrophobic membrane with protein matrix on external part of which the spikes containing glycoproteins and also esterase proteins locate; in internal part of hydrophobic membrane the carrier of its genome, mRNA (it codes 29 proteins) in the form of looped form covered nucleocapsid protein locate [43, 43a]. These strikes interact with membrane apparatus of host cells (i.e. cells of healthy organism) and form the contact with their receptor proteins with following destroy of membrane integrity promoting the penetrating of virus genetic material inside host cells. Taking under consideration that SARS-CoV-1,SARS-CoV-2 destroy mainly on vascular system (lungs, heart, kidneys, eyes and etc.) then we mention that cell membrane of vascular epithelium includes the series of integral proteins (ACE2 is angiotensin-convertingenzyme2, trans-membrane protease, metal-peptidase and others), having the ability to interact with virus protein SARS-CoV-1и SARS-CoV-2(sociability COVID-19 is in more than 10 times higher than for SARS-CoV-1, that is explained by peculiarities of strike protein composition) [43, 44]. Thus, the interruption of virus contact with cell membrane because of structure change of any protein being on strike is the preventive measure for development of infection process [40]. And what is about Se? The fact is that sulphur the content of which in nature from 300 up to 1000 times and in 500 times higher that selenium itself, is the nearest analogue of selenium. The main fact is that Se plays the leading role in formation of protein structure because of SH-groups formation and disulfide bridges (S-S) joining the different groups of protein molecule [2]. Note, that protein disulfide isomerase (PDI) actively take participation in realization of glycoprotein strike contact SARS-CoV-2 with membrane receptors of host cells and their inhibition makes difficult the virus penetration inside healthy cells [40,44].

NATRIUM SELENITE

Sodium selenite presents itself the white crystal powder or crystals dissolved in water. Selenium preparations in small doses act similar to E vitamin, i.e. they take part in processes of tissue breath and oxidation phosphorylation. Sodium selenite has anti-coagulation and anti-toxic properties. As strong anti-oxidant it decreases and breaks the peroxide formation, prevents the overoxidation of fatty acids and accumulation of toxic peroxides in organism and thus normalizes the metabolism. Selenium preparations in big doses are toxic and by their activity are similar to arsenic compounds.

However, in case of Na selenite having the intensive intracellular oxidation metabolism [45-47], it actively reacting with SH-groups of important strike protein SARS-CoV-2-PDI-$(SH)_2$ catalyzes their oxidation by following scheme:

$$\text{PDI-}(SH)_2 + Se^{+4} \rightarrow \text{PDI-S-S-PDI} + Se^{2+}\text{[44]}$$

Thus, in case if the oxidation modification PDI by sodium selenite then this protein loses the ability to interact with integral protein ACE2 of host (organism) membrane cells and the difficulty of contact between virus and healthy cells of organism takes place. There are series of useful properties of sodium selenite in opposition with RNA infection which can be expressed in the form:

1. As it is mentioned above in genome of such viruses as HIV, Ebola, Khant, series of flus, C hepatitis, SARS-CoV-1, SARS-CoV-2 and others are coded such selenoproteins as glutathione peroxidase, thioredoxinreductase, Se-P protein and others. The selective capture of mRNA part responsible for Se-Cys of amino acid for expression of selenoproteins [25, 26], firstly, enzyme thioredoxinreductase which is supplier of protons for necessities of DNA synthesis of healthy cells takes place at penetration in cell of RNA virus host as a result of anti-meaning interactions of mRNA virus and mRNA host cells [23,34]. Thus, as a result the double selenium resource consumption of organism cells necessary for synthesis of both virus selenoproteins and eigen necessities takes place. Thus, selenium deficit state leading to formation of active forms of oxygen [25, 26, 33, 34] and weakening of

immunity on phone of oxidation stress and decrease of organism antioxidation defense appears. In this connection sodium selenite is the successful selenium form which promotes to rapid selenium penetration into cellular structures including the overcoming of hematoencephalic barrier [34, 45-48], that allows us to use sodium selenite for support of essential level of selenoproteins defending organism cells from oxidation stress [12, 48, 49].

2. On model tests with application of tumor cells it is established that sodium selenite suppresses the polymerase reactions of RNA and DNA and thus it can inhibit the tumor growth that shows on the possibility of braking and virus reproduction in host cells [50]. The confirmation of this is the fact that sodium selenite inhibits the reproduction of A group virus already in 80^{th} [50a].

3. Using the known fact that SARS-CoV-1 and SARS-CoV-2 have the series of general genome properties one can make the conclusion about selenium (sodium selenite) influence on development of SARS-CoV-2 infection by SARS-CoV-1analogy. For SARS-CoV-1 it is established that nucleocapsid protein (similarly to SARS-CoV-2) forming RNA fiber, activates the nucleocapsid factor (NF-kB) taking participation in transcription that is accompanied by hard inflammatory process [51,52]. It is seemed that selenium actively inhibits NF-kB protein synthesis, i.e. nucleocapsid factor [53,54], thus it inhibits the virus development in organism cells. On importance of nucleocapsid protein inhibition confirms the fact that it is the key value in transcription processes at HIV infection [55] the genome of which as it is mentioned above has many similar properties with COVID-19 genome.

4. The massive attack of interleukins IL-6 (cytokine storm) on infected organism [56,57] and the destroy of immune response [58] is the one of more dangerous consequences of COVID-19 development. In this context selenium is known as regulator of immune response on all levels: nonspecific, humoral and cellular, simultaneously it limits the activity of T-helpers [59, 60, 61, 61a].

5. As it is mentioned COVID-19 is not only respiratory disease but the vascular one connected with generation of blood supercoagulability [62] and thrombocytopenia formation [63]. Thromboxane formation A2 (TxA2) carrying out the platelet aggregation being the reason of blood coagulation in vessels beginning from smallest alveolar arteries up to big pulmonary ones (effect of “focusing screen”) not only in lungs but in other organs enriched by vessels (heart, kidneys, retina, atrabiliary capsules and others) is in the base of these processes. [63, 64]. Sodium selenite has anti-aggregation effect based on decrease of thromboxane formation [48, 65, 66]. Note that last 30-40 years in whole World the series of commercial semisynthetic and synthetic, organic seleno-containing compounds including Se-Met, Se-Cys in the form of biological additions (BAD) regulating or supplying the necessary selenium status has been prepared [67].

Thus, the totality of mentioned positive properties of sodium selenite gives the possibility for its wide use in the capacity of medioprophylactic means in adjuvant therapy against virus diseases including COVID-19. In spite of advantages of sodium selenite, it has obvious disadvantages: narrow concentration range of therapy action requiring medical attention, fast action effect especially at intravenous introduction (1-2 min) [46], the withdrawal of its significant part from organism not providing the cumulative effect [45, 46, 47, 67].

“EBSELEN” PREPARATION

From above mentioned it is followed that the necessity of study of selenium organic compounds which are seemed more perspective ones in struggle with virus infections because of their low toxicity and action duration [48, 67]. However, not all seleno-organic compounds can successfully apply for prevention and medical treatment of virus diseases including COVID-19 taking under consideration the small time of virus infection development [43]. The fact is that selenium coming to organism from organic compounds passes the complex metabolic way of selenoprotein synthesis taking part in regulation of oxidative, immune, thrombogenic and other processes [61, 67]. As a rule, it stays unavailable until not releases from “organics” transferring into ion form (from Se^{+4} up to Se^{-2}), i.e. up to selenite which is applicable for synthesis of intrinsic organism selenoproteins [45, 61, 67]. It is character that L-selenomethionine which is one of the often met in BAD or vitamin additions less that sodium selenite is applicable for adjuvant medical treatment of virus infections especially COVID-19 because of multi-stage release of selenium from selenomethionine for its resynthesizing into new selenoproteins of organism [67]. In this connection L-selenomethionine or L-selenocysteine yield to sodium selenite which comes to organism by the way of passive transport in short time, it can be used intravenously, intramuscularly, per os being the cheapest and available compendial preparation of Se produced in Russia, Ukraine, Germany and etc. known as commercial name as “Selenase”.

Note that selenoorganic compound with commercial name “Ebselen” synthesized by scientists A.Vendel, P.Graph, M.Parnkhaym and others, has significant effectiveness in group of emphasized compounds. The preparation is seemed the most effective and low-toxic with wide circle of important therapeutic properties: cardiovascular, anticancer, anti-diabetic, anti-bacterial, anti-inflammatory, anti-thrombotic and others. [68, 69]. It is explained by the circumstance that Ebselen has the intrinsic glutathione peroxidase and thioredoxinreductase activity

(peroxiredoxin) carrying out their functions in the absence of these enzymes [70, 71] and also ability to interact with thiol groups in proteins with selenosulfide formation that confirms its action spectrum range on different proteins [72]. Recently the news on anti-virus activity of selenoorganic compound Ebselen on example of HIV and Ebola virus [73], C hepatitis have appeared. Ebselen principal ability and counteraction mechanism to COVID-19 [74,75] has been established in model system. The one of main protein of COVID-19 is the chymotrypsin-like protease [M^{pro}] which has the active cysteine site. This protease splits the long polypeptide on separate polypeptide fragments taking part in replication and transcription processes having in genome. Selenium of Ebselen covalently connects with cysteine of M^{pro} protein and deprives its functional activity on virus genome replication. By other words selenium not splitting from Ebselen molecule blocks its active center M^{pro} [67, 74].

These unique Ebselen properties are the reason for its study and evaluation of its anti-virus effectiveness in comparison with other known preparations which inhibit M^{pro}. Besides, it has strong anti-oxidation properties connected with glutathione peroxidase and thioredoxinreductase activities [68 – 71] under conditions when selenium from Ebselen doesn't consume for natural (intracellular) synthesis GP and TRx because of formed deficit of selenium (that takes place at the use of many other selenium compounds). It protects from oxidative stress being the main reason of virus infection mortality [33, 34, 48, 79-81]. The carried out screening investigations with high transmission capacity showed the some low-molecular ligases probably having inhibition properties among 1000 tested compounds in the capacity of more effective inhibitors M^{pro} acting on catalytic site of this enzyme. Here Ebselen is very interesting [74]. In new investigations it is shown that sensitivity of Ebselen with cavity of catalytic center M^{pro} takes place. The last investigations show that there is unknown site connecting with Ebselen in dimerization region and it is localized between 2nd and 3rd domains of this protein. This means that Ebselen connecting between 2nd and 3rd domains has an allosteric effect which regulates access to catalytic center by the means of interaction by the loop of this protein and this causes the change of its configuration [82]. All these investigations show that Ebselen as the best antivirus preparation can found the wide clinic application.

CONCLUSION

The inorganic compounds (sodium selenide) and organic compounds (Ebselen) can significantly influence on the development of virus infection including COVID-19. The oxidative stress is the one of COVID-19 key damaging elements. One of the main reasons of its activity is that M-RNA COVID-19 has the gens of important seleno-containing proteins (GP, TRx, SelenP) for synthesis and expression of which use the internal resources of selenium, forming its deficit that leads to limit of selenoprotein synthesis of organism. That's why selenium status can have the significant value for both processes of infection beginning and severity of disease carrying out and following complications connected with damage of immune response and development of oxidative stress.

The application of selenium compounds in particular, sodium selenite having the active metabolism in organism sells on all stages of development of virus infection, is the perspective direction in the search of adjuvant means for anti-virus therapy.

Selenoorganic therapeutic compound Ebselen known its unique biological properties is the one of the most perspective anti-virus prepatations the activity of which is based on the inhibition of replication processes especially of transcription of virus genome for clinic use in medical treatment of COVID-19 and its accompanying complications by data of high-velocity screening analysis.

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