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A New Strategy to Protect the Cell from Damage

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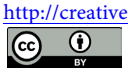

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Abstract

The article theoretically and experimentally substantiates a new method in the free-radical theory of aging, where the target is not the free radicals but the DNA molecules; while radioprotectors are used as antioxidants, previously used to protect the body from radiation damage. A brief overview of various strategies and methods in gerontology is provided. In the quasicrystalline model of DNA, the role of impurity levels is considered. The electronic spectra of DNA bases were calculated by the quantum-chemical extended Hückel method, which gave the DNA band structure. As radioprotectors, when irradiated with laboratory mice, the Po-210 isotope, in particular, orotic, thiouric acid, orotylglycine, and others which has DNA as a target were used. The maximum survival of laboratory mice was obtained by injecting such a radioprotector from a series of selenium derivatives whose n-level was located in the middle of the forbidden band; a comparison was made of the proposed method of using radioprotectors with other methods in gerontology. When using the component selenium orotic acid, Se in combination with hypovitaminosis B13, a significant increase in the rate of tissue regeneration was revealed. So the use of certain radioprotectors as geroprotectors is fully justified; such substances in doses far from lethal have several advantages over other geroprotectors, which at the same time are antioxidants.

Subject Areas

Biophysics, Cell Biology, Pathology, Pharmacology

Keywords

Radioprotector, Forbidden Zone, Gerontology, Polonium, A Dietary Supplement

1. Introduction

Substances that can reliably slow down the aging of the human body, as a sto-

chastic process, are not yet available. The use of drugs such as rapamycin [1] and metformin [2], prolongs the life of model organisms (fruit flies, nematodes, gray rats, house mice, etc.). Synthetic analogues of FGF21 (fasting hormone) may appear [3], and indralin, amifostine, etc. are also used. It is also assumed that there is a genetic program of aging, meaning ageless and even "rejuvenating", *i.e.* returning to previous life cycles, reversing the process of differentiation of cells of organisms.

A new strategy of protection against negative age-related changes is proposed, aimed at protecting against DNA damage. These damages can be caused, among other things, by free radicals (FR). Within the framework of the so-called FR theory of aging [4] [5] [6], it is assumed that aging occurs due to the fact that FR, such as hydroxyl radical NO^-, H_2O_2, singlet oxygen O^- and superoxide O_2^- damages macromolecules—lipids, proteins and, mainly, RNA and DNA [5] [6] [7].

The FR mechanism of aging is confirmed experimentally [8] [9]. The specific life expectancy directly correlates with the content of beta-carotene, alpha-tocopherol and uric acid in the blood serum. In accordance with this, a group of antioxidants is selected from all groups of geroprotectors.

For example, there are data on prolonging the life of animals with increased content of natural substances in the body—the hormone dehydroepiandrosterone, vitamins A, C, E (α-tocopherol), succinic acid, carnosine, carotenoids, and fruit pigments. Vitamins D, K, B5, selenium-containing glutathione peroxidase, and interferon are also mentioned. Synthetic geroprotectors include fullerenes C60, as well as SkQ [10], MitoQ, etc.

The effect of antioxidants is reduced to their reactions with active targets. Thus, vitamin C binds water-soluble FR, b-carotene binds fat-soluble FR, and melatonin binds both.

This article proposes a radical modification of the SR theory of aging. Namely: those antioxidants are selected, the target of which is DNA, both mitochondrial and nuclear.

The direction of protecting DNA from damage was chosen, among other things, due to the fact that DNA damage in the cell is comparable to the aging of polymer chains (for example, in organic glass) under the influence of sunlight. This is an alternative view of the cause of aging of the body as a whole. Such a way of protecting DNA can become essential in the antioxidant system of vitaukt.

D. Sinclair *et al.* investigated a group of genes, sirtuins. Mice without one of the SIRT1 were bred. The mice showed signs of aging, but the levels of all proteins in the cells were normal, except for those encoded by mitochondrial DNA.

It was found that at the molecular level, a key role in the aging process is played by a violation of coordination between the genomes of the cell nucleus and its mitochondria. Decoordination begins with a drop in the level of the compound nicotinamide adenine dinucleotide (NAD), which decreases with age. Without it, the protein encoded by the SIRT1 gene cannot control the activity of

one of the transcription factors (molecules involved in transcription of genetic information with DNA)—HIF. Sirtuins also lose their ability to regulate the processes of apoptosis. The level of HIF increases and this disrupts the normal communication of the two genomes. Over time, because of this, the ability of cells to produce energy suffers, and the body ages.

It was possible to slow down the aging of worms with the help of nicotinamide mononucleotide, a precursor molecule of NAD, which turns into NAD in cells and restores the mechanism of genome communication in the cell. Old mice aged 22 months were injected for a week and found that their muscle tissue became similar to the tissue of 6-month-old rodents, which corresponds to 64 and 18 years in humans.

A link between aging and cancer was also found, since the HIF factor involved in the aging process is also activated in cancer [11] [12].

At the same time, this work does not remove the problem of protecting the DNA itself from damage.

At this time, it has become possible to get acquainted with the materials of the 1st and 2nd admission forms, and wide opportunities have opened up for the use of radiobiology methods in gerontology.

Accordingly, to slow down the aging of the body, it is proposed to use those substances that were previously used as protectors against radiation damage to nuclear DNA. At the same time, for the selection of protectors, it is proposed to use those whose n-levels are "embedded" in the middle of the forbidden zone of the levels of the DNA molecule.

Other strategies also consider, for example, that mitochondria, which produce FR, play a key role in the aging process. It is believed that senile diseases such as diabetes or Alzheimer's disease arise due to irreversible mutations in the DNA of mitochondria.

Another strategy is related to the protection of cells, including DNA, from the effects of FR, by acting on FR (see, for example, [13]), where selenium derivatives are considered as antioxidants). As part of this strategy, attention is also focused on mitochondria due to the fact that active oxidative processes associated with metabolism occur in mitochondria; FR is constantly formed in them, damaging the cell, as well as the DNA of mitochondria. With age, damage and mutations caused by these substances accumulate.

In [13], in particular, it was shown that the use of lipophilic cations for the transport of bioactive molecules into mitochondria significantly increases their efficiency [14] [15]. Thus, MitQ (10-(6-ubiquinolyl)decyltriphenylphosphonium) already in micromolecular concentrations selectively blocks oxidative damage to mitochondria and prevents apoptosis induced by peroxide [16]). However, the difference between anti- and pro-oxidant concentrations of MitQ is small [17].

To reduce the risk of prooxidant activity, it was proposed to use plastoquinone instead of ubiquinone [15]. The synthesized molecule 10E (6'plastoquinonyl) decyltriphenylphosphonium was named SkQ1. This drug prevented, in particular, age-related disorders in outbred mice, and increased survival and average life

expectancy by 92%. But at the same time, it reduced motor activity and endurance, which is natural when the concentration of oxygen radicals decreases. That is, in this case, antioxidants act as traps for FR. At the same time, the authors themselves warn that purging the mitochondria from FR can lead to the degeneration of the cell into a cancerous one.

The proposed method is based on the mechanism of DNA self-replication. This is, in particular, a generalized π-system that "distributes" excitation along the entire length of DNA. It arose in the course of evolution, in the absence of an atmosphere, in conditions of harsh UV and gamma radiation. Therefore, for example, the DNA of blue-green algae has retained the maximum ability to self-repair, which allows them to survive in a nuclear reactor. The tissues of the human body contain approximately 0.1 mg of uranium per 1 kg, *i.e.* a slow-acting radioactive poison. It enters the body together with water and food. If DNA (and the cell) did not have a self-repair system, the existence of the animal world would be impossible (previously, G. M. Barenboim believed that DNA is protected exclusively from Vavilov-Cherenkov radiation that occurs in cells during the decay of a natural admixture of radioactive elements, in fact, as we assume from the entire spectrum of decay).

In the process of self-repair, most of the DNA damage is healed, but a small part is preserved. So, in rats, 10^5 oxidative DNA damages occur daily in each cell. If the rate of self-repair does not reach the rate of damage, the number of spontaneous DNA damage increases [18]. There is a relationship between the lifespan of a species and the rate of DNA repair after exposure to radiation or high-frequency ultraviolet [19].

Radiation damage to the DNA of intestinal epithelial stem cells of mice of different lines and ages is approximately the same, however, the rate of repair of these damages decreases with age. It is obvious that, in general, the ability of cells of cellular organelles to repair single-stranded DNA breaks induced by y-radiation decreases significantly with increasing age of the donor.

2. Semiconductor Model of DNA

Various protectors are used to protect against damage by penetrating radiation. One type of the protectors is those whose target is DNA. They are designed to heal the damage of DNA from the effects of radiation, donating the electron ionized as a result of the gamma quantum of DNA.

A method to describe the effect of gamma radiation on DNA from the point of view of the band theory is known, according to which the DNA macromolecule is represented as a quasi-periodic crystal. The authors considered the zone structure of DNA. It is found that the system of energy levels is formed by the contribution of individual bases, and when the bases interact, each level is eroded, forming a zone. Transitions occur mainly between zones of bases of the same type. The relative displacement of the base levels is negligible.

According to our calculated data, the approximate width of the forbidden

zone is approximately 3.83 eV, according to experimental data 4 eV. Calculations were performed in the π approximation.

When exposed to gamma radiation, after relaxation of the levels, the excitation of π-system of DNA occurs. In this case, electrons from the highest occupied level of the π-system move to its lowest unoccupied, or ionization of the molecule occurs. After the radiation ceases, the excitation migrates along the DNA and leads either to the recombination of electrons and holes, or to damage to the molecule.

The role of DNA n-levels is similar to the role of impurity levels in semiconductors, where the greatest influence on the recombination rate is exerted by deep impurity levels lying near the middle of the band gap—between the valence band and the conduction band of the crystal (for metals, this zone is absent). When moving away from the middle, the probability of transition (dosing) decreases. In this regard, it can be assumed that n-levels are necessary to protect against the excitation of the π-system of DNA.

It should be noted that in the free state, DNA bases are unstable to gamma radiation. It also follows that the cooperation of electronic shells plays a major role in the operation of the safety mechanism.

The electronic levels of a number of known radioprotectors with high radioprotective activity, the target of which is DNA (thiourea, mercamine, ethyron and their derivatives), were calculated by the iterative RMX method. It turned out that the energies of their valence n-levels correspond to the middle or lie close to the middle of the forbidden zone of the DNA π-system. Removal from the middle leads to a decrease in radioprotective activity, going beyond the forbidden zone (serine, paraphenylenediamine, urea, etc.) reduces activity to zero.

So, the most effective are precisely those protectors whose n-levels are "embedded" in the middle, located closer to the middle of the forbidden zone.

3. Experiment

For confirmation, a number of radioprotectors were taken, the target of which is DNA.

Protectors were injected into hybrid mice of the line (SWAhS57B16)F1 weighing 13 - 20 grams, 20 mice in the experiment, by intraperitoneal method 20 minutes before irradiation, in 2% starch solution in equimolar doses of 0.1 - 0.25 lethal dose of LD_{16}. Irradiation was carried out with the isotope Ro-210 (5.3 MeV, at the IGUR installation with a capacity of 0.8 Gr/min.), for 10 minutes.

As we can see from Table 1, the maximum radioprotective activity was detected by selenium orotic acid at $LD_{95/30}$ and thiorothylglycine at $LD_{60\text{-}70/30}$. The ratio of effective and toxic doses for them is 60% - 70%.

The calculation using PMX showed that their n-levels are located most closely to the middle of the DNA forbidden zone of all the listed protectors, the closer the more effective the radioprotector.

Both thiorothylglycine and selenium orotic acid $SeN_2O_3H_3$ are extremely toxic.

Table 1. The dependence of the survival rate of irradiated mice on the proximity of the valence level of the radioprotector to the middle of the band gap of 1.9 eV.

Chemical compound	30-day survival to control, %	n-level measured from the lower limit of the forbidden zone, eV
Orotilglycine	27	1.60
Thiorothylglycine	80	1.96
Orotic acid	20	1.45
Thiorotic acid	18	1.35
Selenium orotic acid	60	1.88

Therefore, there was a hypothesis of the use of two components of the radioprotector, which, possibly, in the digestive tract during an endothermic biochemical reaction with low heat absorption, form the found radioprotector.

Previously, Se was used during various medical procedures in combination with vitamin E, in our case, Se was combined with hypovitamin B13 (orotic acid) at the rate of 1 mcg B13 per 2.4 mcg selenium. The daily dose was set at 100 mcg Se and 40 mcg B13, based on the daily human need for selenium 70 - 100 mcg. 27 subjects who took the supplement for a month were studied, in 85% of cases an increase in the rate of skin regeneration was detected with cuts on the back of the palm almost 2 times (at the end of the month), 100% of the subjects showed an increase in tone.

4. Discussion

A somewhat similar approach was found in [20], where the mechanism of anti-radiation protection of DNA from double breaks was investigated by the formation of intracavity covalent crosslinking of the protector with a biopolymer that stabilizes the structure of the double helix. However, it concerns only double DNA breaks, in our case, the protector counteracts any possible damage to the electronic structure of DNA, and crosslinking with a biopolymer is not required.

The question of the mechanism of convergence of the protector with the target is obvious: the convergence of DNA and the protector has a statistical (Brownian) character and is caused by hydrogen bonding, possibly with the formation of an excimer.

It is also obvious that in DNA models, unlike a semiconductor, where the effect on the recombination rate is determined by the highest probability of transition (the middle of the zone), the interaction of the protector with the DNA π-system is essentially non-averaged, quantum in nature.

At the moment, at least one radioprotector is known to be used as a geroprotector, it is resveratrol.

5. Conclusions

1) The proposed approach use does not deprive DNA of its normal life under

the influence of radicals that are used for protection: the protector affects the DNA itself, which is in danger of damage.

2) Our method does not require strong antioxidants that could reduce the activity of oxygen radicals, or antioxidants with a big difference with pro-oxidants, but those antioxidants whose electronic structure is suitable for DNA bases are needed.

3) Our method does not require cations, the introduction of which in itself has a negative effect on the cell. At the same time, the concentration of the anti-oxidant protector can vary in a wide range.

In addition, when using the above-mentioned geroprotectors-antioxidants, severe side effects are observed: an increase in the frequency of pancreatic islet adenomas (beta-carotene), increased carcinogenesis in the colon (vitamin E), an increase in cholesterol concentration and increased deposition in the aorta (selenium), and induction of liver tumors (dehydroepiandrosterone). There are no such effects in our case.

All the drugs listed in Table 1 have high toxicity and therefore are not applicable as radioprotectors, but they are quite applicable in microdoses as geroprotectants. It is possible to use thiorothylglycine and selenium orotic acid in microdoses of 10-5 LD50.

It is also obvious that there are possibilities to model protectors of other antioxidant series with predetermined properties that would be more accessible and whose n-levels would be embedded in the middle of the forbidden zone [20].

Thus, the use of radioprotectors serving to protect against radiation may prove promising for protecting DNA from damage and, in general, from aging.

4) The combination of selenium and orotic acid can be used as a dietary supplement.

Conflicts of Interest

The authors declare no conflicts of interest.

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