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CURRENT VIEWS ON THE IMPACT OF SODIUM NITRITE AND PONCEAU 4R FOOD ADDITIVES ON THE RETINA AND THE WHOLE BODY

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This article examines the effects of the food additives sodium nitrite and Ponceau 4R on the retina. Both are widely used in the food industry to improve the taste, color, and shelf life of foods. However, their use has raised concerns among scientists and healthcare professionals about potential adverse health effects, particularly on the eyes. Sodium nitrite and its derivatives may cause oxidative stress and inflammation in the retina, which may lead to degenerative changes and vision loss. Although some studies suggest a neuroprotective effect of sodium nitrite, more research is needed to confirm these findings. Ponceau 4R may cause oxidative stress and inflammation in the retina, which may lead to damage to retinal pigment epithelial cells. This could potentially lead to vision loss and other eye problems.

Key words: retina, rats, sodium nitrite, Ponceau 4R, oxidative stress.

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СУЧАСНІ ПОГЛЯДИ НА ВПЛИВ ХАРЧОВИХ ДОБАВОК НІТРИТУ НАТРІЮ ТА ПОНСО 4R НА СІТКІВКУ ОКА ТА ОРГАНІЗМ В ЦІЛОМУ

У статті розглянуто вплив харчових добавок нітриту натрію та Понсо 4R на сітківку ока. Обидві ці добавки широко використовуються в харчовій промисловості для поліпшення смакових якостей, кольору та тривалості зберігання продуктів. Проте їх використання викликає занепокоєння серед науковців та медичних працівників через потенційні негативні наслідки для здоров'я, зокрема для органів зору. Нітрит натрію та його похідні можуть спричиняти окислювальний стрес та запалення в сітківці ока, що може призвести до дегенеративних змін і погіршення зору. Хоча деякі дослідження показують нейропротекторний ефект нітриту натрію, необхідні додаткові дослідження для підтвердження цих даних. Понсо 4R може викликати окислювальний стрес і запалення в сітківці, що може призвести до пошкодження клітин пігментного епітелію сітківки. Це потенційно може спричинити погіршення зору та інші проблеми з очима.

Ключові слова: сітківка, щури, нітрит натрію, Понсо 4R, оксидативний стрес.

The study is a fragment of the research "Restructuring of the organs of the immune, respiratory and excretory systems under the effect of various exogenous factors (monosodium glutamate, sodium nitrite, ethanol, methacrylate)", state registration No. 0121U108234.

Food additives can be of two types: natural and synthetic ones [3]. Natural additives are derived from such food products as fruits, seaweed and minerals. For instance, agar-agar (E 406) and carrageenan (E 407) are obtained from seaweed, while pectin (E 440) is derived from fruits. Synthetic additives can be classified into two groups: synthesized substances that are also naturally present in food, such as ascorbic acid (E 300) and artificial substances that have no natural counterparts, such as butylated hydroxyanisole (E 320). Additionally, there are unauthorized and unapproved food additives that have not undergone the necessary testing. The use of certain additives may be permitted in one country but prohibited in another [5, 8, 17].

The general opinion is that food additives can provoke a range of adverse reactions, such as allergic responses, asthma attacks and gastrointestinal disorders. Media reports frequently highlight relationship between certain food additives and the development of cancerous tumors, allergies and other negative outcomes. However, it is important to recognize that the effect of any chemical substance on the human body depends on several factors, including individual characteristics, the quantity of the substance and the duration of exposure [6].

The findings of the studies have shown that most food additives can be classified as completely safe. The safety of food additives has been established through extensive comparative research, and their use is permitted only after thorough testing and approval by the relevant authorities. Over time, as new toxicological or other data emerge and analytical methods develop, government regulations may be updated.

Some additives that were previously considered harmless (e.g., formaldehyde E 240 in chocolate bars or E 121 in carbonated beverages) were later found to be excessively hazardous and subsequently banned [9]. Moreover, dietary additives that are harmless to one individual may have adverse effects on another. Therefore, it is advisable to limit the consumption of food additives for children, the elderly and individuals prone to allergic reactions [6, 9].

To produce the brand-new food products and achieve specific technological goals, the food industry utilizes hundreds of food additives. In most European countries, more than 540 known food additives are used, while in the United States, the number of food additives, including corresponding mixtures, exceeds 1,500. As of 2019, up to 300 food additives were approved for use in Ukraine. Recently, complex food additives, which are combinations of additives serving identical or diverse technological purposes, have become increasingly common.

The primary requirement for food additives is safety; they must be non-toxic, non-carcinogenic, non-mutagenic and non-teratogenic (i.e., they should not affect fetal development). Additionally, they must not cause allergic reactions. The safety of a food additive depends on its dose, which refers to the amount of the additive consumed by the body daily. Sodium nitrite, monosodium glutamate, and Ponceau 4R pose health risks and are considered dangerous food additives that should be avoided. Many countries have banned most of these additives due to their potential hazards and harmful effects on human health.

In food production, food additives must be used only in the minimum quantities necessary to achieve the intended technological effect, and they must not exceed the established maximum allowable levels (MAL). Additionally, each food additive has a limited scope of use, specifying a particular list of products where the desired technological effect is required. For food additives that pose no risk to human health even in high doses, their maximum content is determined by technological instructions (TIs) and formulations, without the need for specialized instrumental control methods in the final food product [2, 4, 20].

Nitrates (NO3) and nitrites (NO2) are a common group of food additives found in various products, ranging from vegetables to processed meats. Notwithstanding the relative harmfulness of nitrates, they are converted into nitrites during digestion, and the accumulation of significant amounts of nitrites in the body can lead to anemia and an increased risk of developing malignant tumors. The conversion of nitrates to nitrites typically occurs in the stomach, where approximately 5% of nitrates are transformed. However, the remaining nitrates are converted to nitrites only in the distal parts of the intestine, significantly reducing the amount of nitrates absorbed by the body. This process also increases the risk of developing colorectal cancer [1].

Nitrites present in the blood react with hemoglobin, causing the oxidation of iron molecules, which leads to the formation of methemoglobin. This molecule is incapable of transporting oxygen, and its accumulation can result in a dangerous condition that may cause severe fatigue and potential seizures. Infants are particularly at higher risk of complications from nitrate and nitrite consumption. This is because their stomachs have a higher pH level, which promotes greater conversion of nitrates into nitrites. This conversion increases the likelihood of developing methemoglobinemia [7]. Children suffering from nitrate poisoning may develop “blue baby syndrome”, characterized by blue or purple discoloration of the skin due to insufficient oxygen supply, leading to cyanosis.

Sodium nitrite ($NaNO_2$) is a chemical compound that acts as a preservative and color fixative. It appears as a white or pale-yellow crystalline powder that dissolves easily in water. Upon exposure to air, it gradually converts into sodium nitrate ($NaNO_3$).

Sodium nitrite is used as a preservative in meat products. In the acidic medium of the stomach, sodium nitrite reacts with amines to form nitrosamines, or with amides to form nitrosamides. Nitroso compounds are also formed when meat containing nitrites or nitrates is cooked, especially at high temperatures. Sodium nitrite is used in meat processing to preserve the red color of the meat. As a result of

the binding process of nitrates with meat myoglobin, nitrosomyoglobin (MbNO) is formed, which has a pinkish red color and remains unchanged during meat processing [1, 3, 6].

If the daily consumption of E 250 from food does not exceed 0.2 mg/kg, it is considered safe. Sodium nitrite is used as a bronchodilator, spasmolytic and an antidote for cyanide poisoning. It is known that sodium nitrite causes vasodilation, leading to the relaxation of the smooth muscle in arterial blood vessels [1, 17].

Sodium nitrite and its derivatives can have a harmful effect on retinal cells, causing oxidative stress and inflammation. Oxidative stress occurs when an excessive amount of free radicals accumulates in the body – molecules that can damage cellular structures, including proteins, lipids and DNA. In the case of the retina, oxidative stress can lead to damage to photoreceptor cells, which are responsible for light perception.

Studies have shown that nitrites and nitrosamines can cause inflammation in the retina, potentially leading to degenerative changes. For example, one animal study demonstrated that prolonged consumption of nitrites could result in chronic inflammation in the retina, contributing to the development of degenerative diseases such as age-related macular degeneration. This condition is one of the leading causes of blindness in the elderly and is characterized by the progressive deterioration of central vision.

Moreover, some studies have established that nitrites can affect blood circulation in the retina, which may also have negative consequences for vision. Circulatory disturbances can lead to insufficient supply of oxygen and nutrients to the retinal cells, potentially contributing to their degeneration and death.

On the other hand, a study, published in the Journal of Neurochemistry, investigated the neuroprotective effects of sodium nitrite on retinal ganglion cells in a rat model of optic nerve injury. The research demonstrated that treatment with sodium nitrite could promote the survival of retinal ganglion cells and axon regeneration, potentially through its role in nitric oxide signaling pathways. However, it is noteworthy that this study focused specifically on an injury model and may not reflect the effects of sodium nitrite under normal physiological conditions [11, 14].

Nitrites can react with other compounds in the body to form nitrosamines, which are known to have carcinogenic properties. Nitrosamines can have harmful effects on cells and tissues, including the retina, although the specific impact on retinal cells has not been thoroughly studied.

Importantly, the concentration and duration of sodium nitrite exposure can play a significant role in determining its impact on the retina. Controlled and regulated use of sodium nitrite for food preservation is generally considered safe, as it is used in low concentrations and carefully monitored by regulatory agencies. However, excessive consumption or exposure to high levels of nitrite may pose a potential risk.

Scientific studies show that sodium nitrite can have both positive and negative effects on the retina. On the one hand, sodium nitrite may have a neuroprotective effect, protecting retinal ganglion cells from damage. On the other hand, excessive consumption of sodium nitrite can lead to oxidative stress and inflammation in the retina, potentially causing degenerative changes and impaired vision.

Animal studies have shown that prolonged consumption of sodium nitrite can lead to chronic inflammation in the retina, contributing to the development of degenerative diseases such as age-related macular degeneration. This condition is one of the leading causes of blindness in the elderly and is characterized by the progressive deterioration of central vision.

Some studies have shown that nitrites can affect blood circulation in the retina, which may also have negative consequences for vision. Circulatory disturbances can lead to inadequate delivery of oxygen and nutrients to the retinal cells, potentially contributing to their degeneration and death.

Consequently, it is important to continue research on the effects of sodium nitrite on the retina to better understand its mechanisms of action and potential health risks. This will help develop more effective strategies for regulating the use of this food additive and minimize its negative impact on consumer health.

Ponceau 4R, also known as E 124, is a commonly used food additive that has been used to give food products a bright red color since 1910. It is widely used in the confectionery industry, as well as in the production of beverages, ice cream, puddings, desserts and preserves, both alone and in combination with other colorants. This synthetic azo dye has over 100 synonyms and consists of the complex formula $C_{20}H_{11}N_2Na_3O_{10}S_3$, with the chemical name 1-(4-sulfo-1-naphthylazo)-2-naphthol-6,8-disulfonic acid, trisodium salt [5, 12, 17]. Although it is widely used in Europe and Asia, E 124 has not been approved for human consumption in the United States. Some studies suggest that the sodium salts in E 124 are hazardous carcinogens that may lead to malignant tumors [11, 13]. However, there is still no conclusive evidence of the carcinogenicity, hepatotoxicity or neurotoxicity of E 124 when consumed in recommended doses. One

study showed that excessive consumption of Ponceau 4R (E 124) could lead to nephrosis and nephrocalcinosis [12].

Regarding the retina, specific studies on the impact of E124 on this tissue are limited. However, some studies have investigated the effects of other food colorants on eye health. For example, research has shown that certain food colorants, such as tartrazine (E102) and sunset yellow (E110), can induce oxidative stress and inflammation in the retina of animals, potentially leading to retinal damage.

Ponceau 4R may have a negative impact on the retina through several mechanisms. Oxidative stress is one of the main pathways by which food colorants can affect the retina. Oxidative stress occurs when an excessive amount of free radicals is generated in the body, which can damage cellular structures. This damage may lead to inflammation and cell death.

Oxidative stress in the retina can be induced by metabolites of Ponceau 4R, which are capable of interacting with cellular components, leading to the formation of reactive oxygen species (ROS). ROS can damage cell membranes, proteins and DNA, resulting in inflammation and cell death. In the retina, inflammation can contribute to the development of degenerative diseases such as age-related macular degeneration and diabetic retinopathy. These diseases are among the leading causes of blindness worldwide.

Studies have shown that Ponceau 4R may have a toxic effect on retinal pigment epithelial cells. The retinal pigment epithelium plays a crucial role in supporting the function of photoreceptors and protecting the retina from light-induced damage. Toxic effects on these cells can impair their functions, leading to degeneration of photoreceptors [18].

The study published in 2006 found that Ponceau 4R, along with other food colorants, could cause damage to retinal pigment epithelial cells. This damage may lead to oxidative stress and apoptosis (programmed cell death), which can ultimately impair vision [15].

Some studies show that Ponceau 4R may affect the blood circulation in the retina, which could have negative consequences for vision. Disruptions in blood flow can lead to insufficient delivery of oxygen and nutrients to retinal cells, contributing to their degeneration and death. This is particularly concerning for patients with existing eye diseases, such as diabetic retinopathy, where the retinal blood supply is already compromised.

Since the 1970s, scientific literature has periodically linked food colorants to negative effects on child development, particularly with attention deficit hyperactivity disorder (ADHD) [6, 8, 17]. This has led some countries to include the Ponceau 4R (E 124) on lists of banned substances [6, 17].

In September 2009, the European Food Safety Authority (EFSA) adopted a resolution to reduce the acceptable daily consumption of E 124 (Ponceau 4R, bright red) from 4 mg/kg to 0.7 mg/kg body weight per day, despite the lack of conclusive evidence regarding the potential for food additives to cause behavioral disorders in children [6].

However, recent studies have demonstrated a less clear-cut view on the use of food colorants. For example, researchers from the Department of Pediatric Nutrition and Gastroenterology at Trousseau Hospital and Sorbonne University in Paris (France) conducted a study involving 23 patients and found that food additive allergies remain relatively rare. Medical professionals and parents should be reassured about the low risk of food colorant intolerance or allergies. On the other hand, in countries like the United States, Finland, Norway, and others, E124 is included in the list of banned substances due to its potential carcinogenic properties. It is considered to be a strong allergen and can trigger anaphylactic shock or asthma attacks in individuals with aspirin intolerance. Additionally, it is associated with increased hyperactivity in children.

Although most research focuses on the effects of food colorants on children's behavior and hyperactivity, some studies have explored their potential impact on the eyes. However, it is important to note that the available literature on this topic is limited, and additional research is needed to fully understand the effect of E124 on the retina.

Another study published in 2022 focused on the impact of food additives, including E124, on visual processing and attention in children. The research showed that food additives, including colorants, may have a negative effect on visual attention and perception, which could indirectly influence the function of the retina. [18].

Noteworthy, the concentrations of E124 used in these studies were higher than those typically found in food products. Nevertheless, these studies raise concerns about the potential negative impact of food colorants on retinal health.

Generally, the existing literature on the direct impact of E124 on the retina is limited. Additional research is needed to gain a deeper understanding of its potential effects on the cells and functions of the

retina. Moreover, regulatory bodies continuously monitor the safety of food additives, including food colorants, and set recommendations regarding their permissible levels in food products [11].

Conclusion

This article provides a detailed analysis of the impact of sodium nitrite and Ponceau 4R food additives on the retina. Both of these additives are widely used in the food industry to improve the flavor, color and shelf life of products. However, their use raises concerns among scientists and medical professionals due to potential negative health effects, particularly for the eyes. Sodium nitrite and its derivatives can induce oxidative stress and inflammation in the retina, potentially leading to degenerative changes and impaired vision. Although some studies suggest a neuroprotective effect of sodium nitrite, further research is needed to confirm these findings. Ponceau 4R can induce oxidative stress and inflammation in the retina, which may lead to damage to the retinal pigment epithelium cells. This could potentially result in impaired vision and other eye-related issues.

Further research is needed for a more comprehensive understanding of the mechanisms of action of sodium nitrite and Ponceau 4R on the retina, as well as to assess their long-term effects on health. This will help develop more effective measures to protect consumer health.

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