Analysis of the Influence of Nitrite for Public Health

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Abstract: Nowadays, it is necessary to study whether nitrite should be limited strictly or used normally, since nitrite has both benefits and probable harms. Researchers hold different opinions of nitrite, including if nitrite should be ingested by people, making people confused on who to believe and which instruction to follow. Thus, the author conducts this study to have an overview on the previous literature and analyzes the related information in order to give suggestions to people. Through the analysis, it is concluded that nitrite has advantages of curing cardiovascular disease, and defensing bacteria. Additionally, it has controversial harms of causing cancer and deformity, as well as the doubtless harm of nitrite poisoning. To deal with the benefits and harms of nitrite, people should ingest nitrite properly and the government need to take actions to reduce nitrite pollution.

1 INTRODUCTION

Nitrite commonly forms in daily food, especially vegetables, barbecue, and pickled food. With the development of technology and the improvement of living standard, people have progressively paid more attention to food safety, so nitrite in food becomes one of the hot spots. Nowadays, it is controversial that if nitrite should be limited strictly or used normally since nitrite is both beneficial in some aspects, and has some uncertain harms, such as causing cancer and deformity. To be specific, news and some articles provided by social media tell people to focus on the carcinogenicity and teratogenicity of nitrite, and provide advice, such as warning people not to drink water that has been boiled for several times, which contains more nitrite than normal water. What is more, there are lots of studies and experiments to prove that nitrite does not cause cancer and deformity, but has plenty of benefits. Under this circumstance, people hesitate about which opinion to believe so that they may not have the proper strategy to control nitrite. Therefore, it is necessary to review the positive and negative influences of nitrite, and give some suggestions on how to deal with nitrite when we have not solved this controversy. This paper would elaborate these points to help people understand nitrite more clearly, and tell individuals as well as departments of government to control nitrite to maximize the benefit and minimize the probable harms.

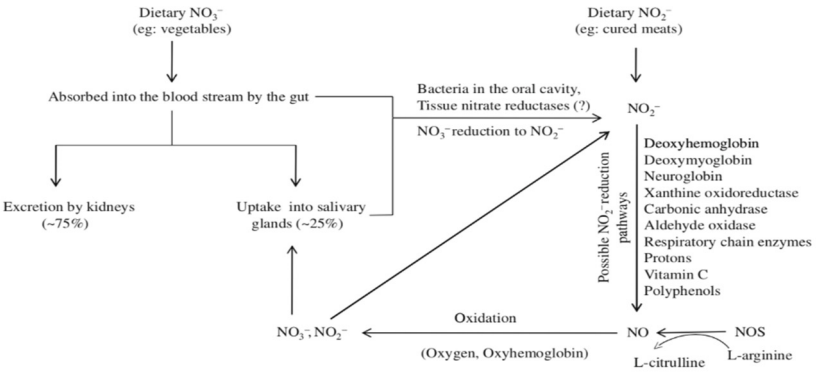

Figure 1: Schematic presentation of nitric oxide (NO) generation and metabolism in the body (Machha, Schechter 2011).

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2 ANALYSIS OF THE BENEFITS AND HARMS OF NITRITE

2.1 Benefits of Nitrite

2.1.1 Management of Cardiovascular Disease

As can be seen in figure 1, nitrite can be reduced to be NO in human body. Up till now, scientists have found many ways to reduce nitrite to be NO. For example, nitrite can be reduced by deoxyhemoglobin, deoxymyoglobin, xanthine oxidoreductase, cytochrome P450 enzymes, mitochondrial respiratory chain enzymes, aldehyde oxidase, carbonic anhydrase, acidic disproportionation, and reducing agents (e.g. ascorbate, polyphenols), which only have high activity in the low-PH and low-oxygen condition (Machha, Schechter 2011). Additionally, arterial venous gradient of nitrite in human forearm circulation shows that nitrite is metabolized to NO across physiological pH and oxygen level (Cosby, Partovi, et al. 2003). Thus, NO, reduced from nitrite and can be formed in low-oxygen condition, is the substitution of endothelium-derived NO, which is synthesized from the amino acid L-arginine by the eNOS enzyme with oxygen. Thus, there would be more NO in cardiovascular system if people ingest nitrite.

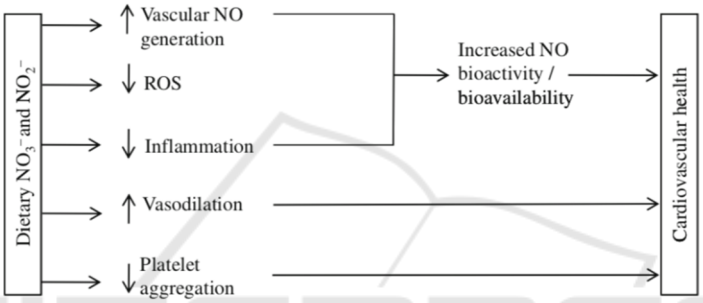

Figure 2: Schematic presentation of potential mechanisms by which dietary nitrite and nitrate could modulate cardiovascular health (Machha, Schechter 2011).

NO plays a significant role in improving the endothelial function since NO can help to maintain the vascular homeostasis. To be specific, as can be seen in figure 2, NO can control smooth muscle cells and circulating blood cells to manage the proliferation of smooth muscle cell, activity of platelet, and vasodilation of blood vessels (Naseem 2005). Hence, the lack of NO would cause endothelial dysfunction, leading to the disruption of vascular homeostasis, and then result in many cardiovascular problems. On the contrary, sufficient amount of nitrite would make cardiovascular diseases below to be cured.

As for thrombus, abnormal aggression of platelet would lead to thrombus, which would contribute to the cerebral thrombosis, myocardial infarction, or ASO. Fortunately, the intake of nitrite can inhibit the aggregation of platelet (Johnson et al. 1990). As for Myocardial ischemia, reperfusion therapy is one of the most effective treatment to decrease the size of myocardial infarction area by making blood go back to the heart. However, reperfusion therapy would cause myocardial damage, which is a very serious problem, leading to heart failure, cardiac fibrosis, and even sudden death. Recent research display that nitrite would reduce the damage to heart. For example, Webb et al. found that the retrograde perfusion with nitrite can decrease the myocardial infarction area by 60% during the treatment of retrograde perfusion (Webb et al. 2004). Hypertension has been one of the commonest disease in cardiovascular diseases. Nowadays, plenty of people, especially the middle-aged and the elderly, are suffered or even die because of hypertension. As an important way to cure hypertension, the treatment of nitrite works out pretty well. Scientists found that 18.8 mg of nitrate per kilogram body weight per day, which would be transformed to nitrite inside body (Feng 1983), would decrease diastolic blood pressure by 4.5 mm (Hg Sobko et al. 2010).

2.1.2 Defense against Bacteria

Nitrite can inhibit the growth of anaerobic bacteria, such as Achromobacter, Aerobacter, Escherichia, Flavobacterium, Micrococcus, and Pseudomonas. The function of nitrite of defensing against bacteria, in my opinion, can be divided into three parts—oral cavity, gastrointestinal tract, and skin. As for oral cavity, 25% of the intake of nitrate into human body

would be secrete to oral cavity, and then be reduced to nitrite by symbiotic bacteria in mouth. Because of the antibacterial function of nitrite, many bacteria in mouth can be inhibited. As for gastrointestinal tract, acidic environment provided by gastric acid would acidify nitrite, helping to kill bacteria. To illustrate, Dykhuizen et al. conducted experiment that make Yersinia enterocolitica, Salmonella Enteritidis, Shigella sonnei, and Escherichia coli O157 to be exposed different concentration of nitrite and different PH. As a result, they found that the acidic condition and nitrite would cooperate to kill pathogen (Dykhuizen et al. 1996). Skin is also a weak acidic environment because nitrite would be released to the surface of skin with sweat, and nitrite can play a role in defensing bacteria on skin.

2.2 Harms of Nitrite

2.2.1 Carcinogenicity of Nitrite

The carcinogenicity of nitrite is still sort of controversial. Some scientists are big supporters of the opinion that nitrite would lead to cancer. First, the mechanism of nitrite is very clear. Nitrite does not cause cancer directly, and most of the intake of nitrite would be excreted out of body along with urine. Nevertheless, under acidic condition (PH 1-4) some of nitrite would decompose into nitrous acid, which would then decompose into nitroso due to the instability. After this, nitroso would combine with secondary amine, a kind of metabolites of protein, to synthesize nitrosamine, which is a sort of very strong carcinogen. Nitrosamine would methylate guanine of RNA and DNA to make mutation occur in cells (Zhang et al. 2015). Second, some experiments, such as the experiment conducted by U.S. National Toxicology Program, showed that although there was no evidence showing that the sodium nitrite had carcinogenic activity in the group of female F344/N rats and male B6C3F1 mice, they found that maybe the carcinogenic activity displayed in the group of female B6C3F1 mice according to the positive trend in the incidences of squamous cell papilloma or carcinoma (combined) in the forestomach (Program 2008).

Other scientists believe that nitrite does not have the property of carcinogenicity, so they contradicts the opinion above respectively. First, the formation of great amount of nitrosamine is not convincing. Specifically, nitrite requires nitrite reductase from certain bacteria to catalyze the reaction of synthesis of nitrosamine, but healthy people have very little this sort of bacteria in their stomach. What is more, 500 mg vitamin C can reduce the formation of nitrosamine in stomach reduce by 99%, so the everyday diet would almost prevent the formation of it. What is more, attributing to the acidic environment in stomach, nitrite would be quickly reduced into NO, and then released out of body (Griesenbeck et al. 2009). Therefore, it is no need to worry about the nitrosamine transformed from nitrite. Second, the experiment of rats and mice is not convincing either. This research only offer the evidence of carcinogenicity in forestomach of female B6C3F1 mice, but not offer evidence of carcinogenicity in other organs or tissues in both female and male mice and rats (Bryan et al. 2012). Third, as evidenced by information in figure 3 shown below (Bryan et al. 2012), scientist indicates that the a majority of research proving that nitrite is carcinogenicity was conducted several decades ago, and most of more recent, and better-designed studies showed that nitrite was not related to cancer.

However, some other scientists raises new point that nitrite does not cause cancer, but induce cancer (Huang et al. 2009). Specifically, before the formation of tumour, cancer cells has already attain denitrification gene from some symbiotic bacteria with anaerobic metabolism in human body, and then survive as cancer stem cells. In certain condition, these cancer stem cells would move to tumour, and the gene with the function of denitrification would be activated. These cells would choose nitrite respiration to adapt to the microenvironment surrounding the tumour. Hence, as the source of nutrient of cancer cells, nitrite may promote the growth of them, but not cause cancer. However, this idea does not have enough data, or material supporting it so that the truth of this theory is doubted.

2.2.2 Teratogenicity of Nitrite

Like the carcinogenicity, the teratogenicity of nitrite is also controversial. Many materials show the teratogenicity of nitrite. For example, $NaNO_2$ would damage the DNA of supporting cell of testis when the dose of $NaNO_2$ is larger than 150 μg /ml (Ren 2007). Some other information disproves the teratogenicity of nitrite. For instance, 0-100 mol/L sodium nitrite under neutral condition would not hurt DNA of epithelial cells in stomach. Only when PH falls to 4.2 and the dose of sodium nitrite is more than 50 mmol/L, the DNA might be damaged (Smith et al. 2006). Thus, people cannot reach that strict standard of environment in their daily life, so the harm stemming from the teratogenicity would not occur.

	Duration	# Males	# Females	Nitrite levels (ppm)	Vehicle	Not carcinogenic	Carcinogenic
A. Rat studies							
Shank and Newberne (1976)	130 weeks	96?	?	1000	Rat chow	X	X?
Matsukura et al. (1977)	16 months	4	0	1600	Pellet diet		X
Ivankovic (1979)	10 months	0	?	50 mg/kg/d	Feed	X	
Krishna Murthy et al. (1979)	1 yearr + 120 days	20	20	5000	Feed	X	
Aoyagi et al. (1980)	92 weeks	24?	?	800, 1600	Pellet diet	X	X
Mirvish et al. (1980)	Lifetime, 120 weeks max	22	23	3000	Water	?	?
Lijinsky et al. (1983)	2 years	24, 24, 24	24, 24, 24	2000	Diet – 48, water – 24	?	?
Lijinsky (1984)	2 years	24	24	2000	Diet	?	?
Olsen et al. (1984)	132 weeks	70,60, 60,66	70,60, 60,66	200, 1000, 4000 in cured meat formula	Cured meat		X
Lin and Ho (1992)	10 months	?	?	3000	Squid or wheat based diet	X	
Hirose et al. (2002)	52 weeks	0	10	2000	Water	X	
Miyauchi et al. (2002)	36 weeks	10	0	2000	Water	X	
Yada et al. (2002)	28 weeks	5	0	500	Water	X	
Ichihara et al. (2005)	8 weeks	15	0	1000	Water	X	
Ishii et al. (2006)	0.5 d–2 weeks	42	0	2000	Water	X	
Kitamura et al. (2006b)	48 weeks	0	10	2000	Water	X	
Kitamura et al. (2006a)	29 weeks	18,20	?	1000, 2000	Water	X	
Kuroiwa et al. (2007)	42 weeks	10	0	2000	Water	X	
Kuroiwa et al. (2008a)	32 weeks	9	0	2000	Water	X	
Kuroiwa et al. (2008b)	12,52,78 weeks	5, 5,15	0	2000	Water	X	

Figure 3: Animal Toxicological Studies of Nitrite Carcinogenicity with Serious Methodological Limitations (Bryan et al. 2012).

2.2.3 Nitrite Poisoning

Nitrate poisoning, also called enterogenous cyanosis, resulted from too much intake of nitrite or nitrate (a great part of nitrate would be reduced into nitrite in human body). 0.3-0.5g nitrite would cause nitrite poisoning, and more than 3g nitrite would cause death (Ye 2007). After nitrate gets into human's body, it would react with ferrous ion in hemoglobin to oxidize normal hemoglobin into hemoglobin, which does not have the ability of carrying oxygen (Ye 2007). In this regard, all the tissues and organs in human body would confront oxygen deficit, leading to the symptoms mentioned above.

3 MEASURES OF CONTROLLING NITRITE

According to the benefits and harms of nitrite above, it is difficult to completely prohibit the use of nitrite because of its benefits in treatment and prevention of cardiovascular diseases, and the function of defensing bacterial. Moreover, we cannot intake nitrite as much as we want since scientists are not sure if nitrite has car and tera properties, and too much nitrite would lead to poisoning. Thus, some instructions or measures are needed to avoid the possible harms and attain benefits.

3.1 Distinguishing Susceptible Population

Given the probable harms of nitrite because of the doubted carcinogenicity and teratogenicity, it is necessary to find susceptible population, and develop special diet standard for them to avoid these harms (Huang et al. 2009). Susceptible population here might include ones who have medical history of cancer, especially gastric cancer, in family, ones who have serious stomach problems, and so on. As for these susceptible population, they should follow their own diet standards, such as avoiding consuming barbecue and pickled food, which contain relatively high amount of nitrite. If possible, they should also remember to blanch some vegetables high in nitrite before cooking, like spinage, to reduce nitrite.

3.2 Avoiding Excessive Intake of Nitrite

Too much intake of nitrite would lead to nitrite poisoning, so all of people should pay attention to the amount of nitrite they ingest. For instance, people should not purchase pickled food without having labels of expiration rate, and ingredient list, in informal stalls. According to the analysis of test result of nitrite content in cooked meat product in Zhoukou in 2014-2015, products with nitrite beyond the standard have a proportion of 34.87% among all the products, and the maximum nitrite content is 1370mg/kg (Zhang, Lu, Sun 2017). If people consume plenty of packaged food like these, they might be suffered from nitrite poisoning.

3.3 Control of Nitrate Pollution in Vegetables

In most of areas in China, nitrates (which would be reduced into nitrite) in several kinds of leafy and root vegetables with relatively high consumption are much higher than normal, and the one with highest content is 9 times as standard (Ye 2007). Under this circumstance, it is necessary for the governments and organizations to control nitrate pollution in vegetables. Here are some advice: Governments can request farmers to select vegetables species which cannot accelerate much nitrate; the Bureau of Agriculture can come up with new way to use fertilizers, such as coordinating nitrogen fertilizers with organic fertilizers.

3.4 Dietary Intervention of Nitrite

Nitrite has the ability of curing cardiovascular diseases, so doctors can design special daily diet plans for patients who suffer from cardiovascular diseases, especially hypertension. According to different conditions, doctors can adjust the intake of nitrite for patients in everyday meals.

4 DISCUSSION

This paper analyzes both the benefits and the probable harms of nitrite comprehensively, and provide some measures to control the use of nitrite to not only prevent people from harms, but also take advantage of nitrite. According to the evidence provided by past papers, the opinion that nitrite does not have carcinogenicity and teratogenicity is more convincing because of the clear, logical arguments, and plenty of accurate date from experiments. Nevertheless, the evidence supporting the carcinogenicity or teratogenicity of nitrite is sort of insufficient, and has some holes. Although perhaps nitrite may not cause cancer and deformity, people should still pay attention to their intake of nitrite since no one has offered the perfect experiment and research result to make sure that nitrite would not lead to cancer, deformity, or maybe some other illness that scientists have not found. Therefore, scientists should continue to devote great efforts to the controversy or carcinogenicity and teratogenicity of nitrite in the future in order to understand the property of nitrite in depth so that people can ingest nitrite properly, and then achieve healthier life.

The influence of nitrite is only one part of food safety. Food safety nowadays is a serious problem in many countries. Thus, governments should introduce new policies to control food products, and supervise food hygiene; organizations and social medias should popularize knowledge of food safety; individuals should follow the instructions and pay more attention to their everyday food. The more everyone devote to food safety, the healthier people should be.

5 CONCLUSIONS

Nitrite has benefits of curing cardiovascular disease, and defensing bacteria. What is more, it has controversial harms of causing cancer and deformity, and the doubtless harm of nitrite poisoning. To deal with the benefits and harms of nitrite, people should follow instructions to ingest nitrite properly, and government need to take actions to reduce nitrite pollution. Additionally, scientists should continue to explore the carcinogenicity and teratogenicity of nitrite, in order to make measures of controlling nitrite more impeccable.

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