

September 2019

Nice Traits of Nitrates

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Recommended Citation

Lokkesmoe, Ryan K. (2019) "Nice Traits of Nitrates," *The Idea of an Essay*: Vol. 6 , Article 23.
Available at: https://digitalcommons.cedarville.edu/idea_of_an_essay/vol6/iss1/23

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Ryan Lokkesmoe

Nice traits of Nitrates

Everyone will, if they live long enough, die from cancer. In this brave new world, there are countless dangers that arise which mankind has never had to deal with previously. For millennia people have faced starvation, violence, and disease, with varying levels of success. Today, we continue to fight these same battles, yet in the developed world, humanity has pushed its life expectancy so far that a host of unexpected problems have arisen. Dying at unprecedented rates from cancer and heart disease, people are, for the first time in human history, living long enough for these diseases to take effect.

The purpose of medicine has always been to delay the inevitable; holding back the onslaught of time for as long as possible. Today the war is waged on the ground of molecular biology; more than ever, the complex interactions of the many nutrients, metals, and organic chemicals that we put in our bodies must be considered. One of these nutrients that has recently come into the spotlight is nitrate.

Found naturally in many vegetables, especially green leafy vegetables, and commonly used as a preservative in meats, nitrate is in the peculiar situation of being both “natural” and “additive”. To properly discuss this interesting compound, some organic chemistry background is necessary. Nitrates consist of a nitrogen atom, which is bound to three oxygen atoms, thus allowing for a “resonance stabilized” negative charge. Without delving into the

mechanics of resonance, suffice it to say that molecules that have resonance are stable even when charged, making them more inert.

When nitrate is “reduced”, electrons are added and bonds are broken with oxygen, leading to nitrite, which has the formula NO_2^- , since an oxygen was removed. Nitrite is capable of resonance, but not to the same extent as nitrate, and therefore it is more unstable. Further reduction leads to nitric oxide, or NO , which is a radical (has an unpaired electron), has negligible resonance, and is highly unstable. Nitric oxide is transient (only lasts for a short while) but has numerous important roles in physiology, which will be discussed at length shortly.

According to Lundberg, Weizberg, & Gladwin’s influential analysis in 2008, nitrate has previously been regarded as an inert oxidative end product of nitric oxide metabolism (oxidation is the name for what happens to the molecules that reduce nitrate) or a potentially dangerous residue in food (p. 156), but lately it has received much more attention. Although there are still critics, the scientific community is beginning to agree that the archaic view of nitrate is not sufficient to explain its sundry effects. Through the next several pages, this essay will demonstrate that nitrates hold exciting potential as a safe and effective cardiovascular protectant by discussing their role in methaemoglobinaemia and the formation of N-nitroso carcinogens, their biochemical and physiological effects, and the therapeutic or supplementation applications of nitrates that are developing.

Methaemoglobinaemia, a truly daunting word, simply refers to the presence of methaemoglobin in the blood. This

presence comes from the oxidization of the iron in hemoglobin to Fe^{3+} by nitrite. (Lundberg et al., 2008, p 165). Unlike hemoglobin, methaemoglobin is incapable of carrying oxygen, and so, if a considerable amount is formed, the body's tissues won't receive the necessary nutrients from circulating blood. Naturally, this is a serious concern, but numerous peer-reviewed studies have indicated that dietary nitrate intake cannot be linked with any significant rise in methaemoglobinaemia (Mensinga Speijers, & Seulenbelt, 2003; Pluta, Dejam, Grimes, Gladwin, & Oldfield, 2005; Velmurugan et al., 2016). This then presents a false danger and no real threat besides the fear of a long word.

The second concern often cited when discussing nitrates is the potential for the formation of N-nitroso carcinogens. Many would be quick to avoid nitrates completely at the mere mention of a connection with cancer, but such a hasty conclusion is unfounded. While nitrites (derived as we have seen from nitrates) do have an *in vitro* capacity to form nitrosamines and nitros-amides when mixed with secondary amines or N-alkylamides, there is uncertainty as to whether this occurs *in vivo*. Additionally, despite a vast number of studies, no clear evidence has actually linked dietary nitrate consumption to an increased chance of any form of cancer (Mensinga et al., 2003, p. 46; Ward et al., 2005).

In fact the opposite has been observed, with several experiments linking high vegetable—and thus high nitrate—diets to a reduced overall risk of cancer (Mensinga et al., 2003; Lee & Chan, 2011; Bedale, Sindelar, & Milkowski, 2016). Whether this is a result of other beneficial nutrients in vegetables or nitrate is

unclear, but in any case, the increased nitrate intake did not lead to cancer. Thus, it is safe to say that nitrate rich diets are at the very least, safe. Neither methaemoglobinaemia nor N-nitroso carcinogens pose any serious threat to the consumer and should not be feared.

It is helpful in this discussion of safety to consider the normal biochemical role that nitrate plays in the body. For proper function, blood vessels require nitric oxide (NO), usually synthesized by endothelial cells (Palmer, Ashton, & Moncada, 1988, p. 664), through the nitric oxide synthase pathway. This pathway converts L-arginine to nitric oxide, and is dependent on the presence of oxygen. Acting as an antiplatelet, influencing blood vessel diameter, and controlling inflammation, NO keeps blood vessels open, and helps to ensure that all tissues receive adequate amounts of oxygen.

As was discussed previously, NO is a radical, and is therefore very short lived, influencing only the cells in the immediate vicinity of its release. This allows nitric oxide levels to be adjusted in each tissue as needed, increasing blood flow to parts of the body that are using extra oxygen, and allowing constriction of vessels in areas that have plenty of nutrients. As a result, nitric oxide synthesis is a continual and never-ending process. Under normal conditions, this poses no problem, but since the NOS-dependent pathway requires oxygen, in intensely exercising muscle, the process cannot keep up (Lundberg et al., 2008, p. 157).

Enter nitrate. Through a pathway that is independent of NOS synthase and doesn't require oxygen, nitrate is reduced to

nitric oxide, providing for the tissues that otherwise would quickly become hypoxic. “In this sense, NOS-independent NO formation can be viewed as a back-up system to ensure that there is sufficient NO formation when oxygen supply is limited, which is analogous to the complementary role of anaerobic glycolysis in energetics” (Lundberg et al., 2008, p. 156). Thus, nitrate acts as reservoir of nitric oxide.

How does this pathway work? The nitrate consumed in the diet is absorbed in the small intestine, and up to 25% is transported to and excreted by the salivary glands, where it is concentrated in the oral cavity. Once in the mouth, nitrate is reduced to nitrite by certain commensal bacteria and swallowed. This nitrite is then circulated and can be converted to NO with the help of vitamin C and polyphenols as needed in various tissues (Lundberg et al., 2008, p. 159).

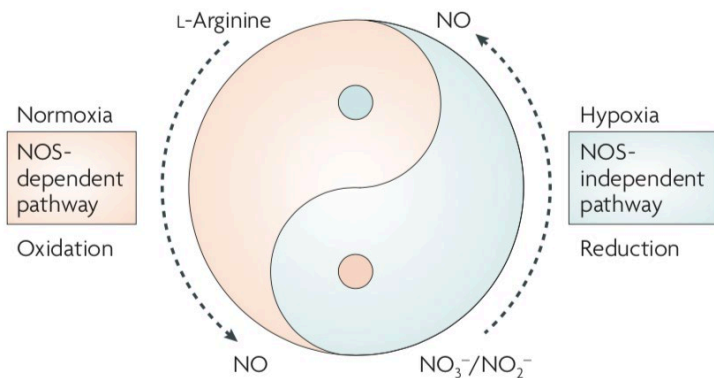


Figure 1. Two parallel pathways for NO generation (Lundberg et al., 2008, p. 158).

Of import is the role of the oral microbiome in this process. In order for nitrate to become biologically active it must be converted to nitrite, and this conversion is only accomplished through the facultative anaerobic commensal bacteria in the mouth (Bryan, Tribble, & Angelov, 2017). This becomes useful when testing for the effects of nitrate. If supposed effects are reduced when the microbiome is disrupted, then it is likely that nitrates and nitrites are at play, but if no change occurs, then nitrates may not be involved. Additionally, nitrate supplementation can be supposed to favor the growth of certain bacteria, which should result in a shift of the oral microbiome if the nitrate is being effectively reduced, providing another confirmation test.

If nitrate is so important, we should expect negative effects of dietary deficiency, and this is precisely what is observed. Kina-Tanada, et al. (2017) performed a study on the effects of diets that contain no nitrate on mouse models. Not surprisingly, the mice that did not receive nitrate began to experience some unfortunate conditions. As soon as three months on the new diet, the mice experienced visceral adiposity, dyslipidemia, and glucose intolerance (buildup of fat around internal organs, excess lipid blood levels, and negative reactions to sugar).

Eighteen months into the study, these deficient mice developed hypertension, insulin resistance, and impaired endothelium-dependent reactions to acetylcholine, while also gaining weight, despite receiving the same caloric levels as the nitrate-rich mice. By 22 months, the diet led significantly to death, usually through cardiovascular disease (Kina-Tanada, et al., 2017,

p. 1149). As further confirmation, these results were reversed by treatment with sodium nitrate (p. 1138).

These pyric effects are not only detected only in mice, however. A prospective cohort study in 2017 of 1226 initially healthy women explored the progression of arteriosclerotic vascular disease (ASVD) over the course of 15 years, comparing it to vegetable intake. Diets rich in vegetables, and therefore rich in nitrates (fig. 2), were correlated with lower ASVD mortality (fig. 3) and lower all-cause mortality independently of lifestyle and cardiovascular disease risk factors. These data suggest strongly that diets high in vegetable derived nitrate provide numerous vascular health benefits, cumulating in greater survival rates (Blekkenhorst, et al., 2017).

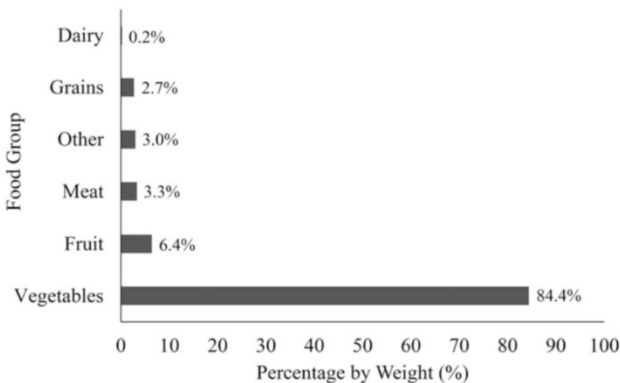


Figure 2. Contribution of nitrate intake (milligrams/day) from each food group (Blekkenhorst, et al., 2017, p. 213).

Results like these are not surprising when one considers that vascular dysfunction can be defined functionally by a reduced

availability of nitric oxide, typically by dysfunction in the NOS-dependent pathway (Velmurugan, et al., 2016, p. 26). Many recent studies have been focused on determining means to exploit the relationship between NO and nitrate. Organic nitrates, such as nitroglycerin are often used to treat hypertension, but could inorganic dietary nitrates have similar uses? Potentially causal relationships between nitric oxide levels and diseases such as insulin resistance, ischemic heart disease, and hypertension (Kobayashi et al., 2015, p. 4911) have led to “clear and delineated doses of both nitrite and nitrate that provide indisputable evidence of promoting health and even treating serious medical conditions” (Bryan and Ivy, 2015, p. 650). What are some of the observed benefits?

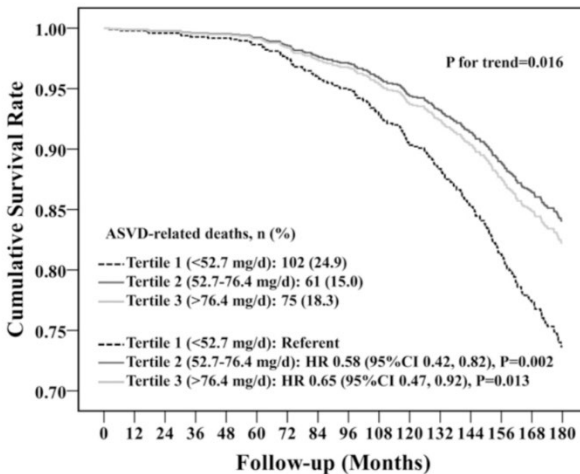


Figure 3. Multivariable-adjusted cumulative survival curves for atherosclerotic vascular disease mortality according to tertiles of vegetable nitrate intake (Blekkenhorst, et al., 2017, p. 214).

Most importantly, nitrate intake is thought to potentially lower blood pressure (Bryan et al., 2017; Lovegrove et al., 2017), although some claim that sulfate is also necessary for this effect (Kuhnle, Luben, Khaw, & Feelisch, 2017). Lowering systolic pressure by just 5mmHg reduces the prevalence of strokes by 35% and ischemic heart disease by 21% (Bryan & Ivy, 2015, p. 650), as well as slowing the progression of atherosclerosis. Other benefits could include: improved vascular function, lower inflammation, improved exercise capacity, improved mitochondrial function, lower triglycerides, and less heart attacks (p.650). The authors conclude that the cardiovascular benefits far outweigh any potential risks (fig. 4).

Given the few primary prevention options for cardiovascular disease (Velmurugan, et al., 2016, p. 25), a new nitrate-based drug could have extraordinary benefits. Supplementation in individuals with hypercholesterolemia was shown to result in an increase in flow-mediated dilation, which indicates improved vascular function (p. 35) and these improvements were linked with changes in the oral microbiome, confirming the role of nitrate. With these encouraging results, the authors claim that dietary nitrate may be used “as a safe, well-tolerated, and potentially powerful prevention strategy in CVD in individuals with early vascular dysfunction” (p. 36).

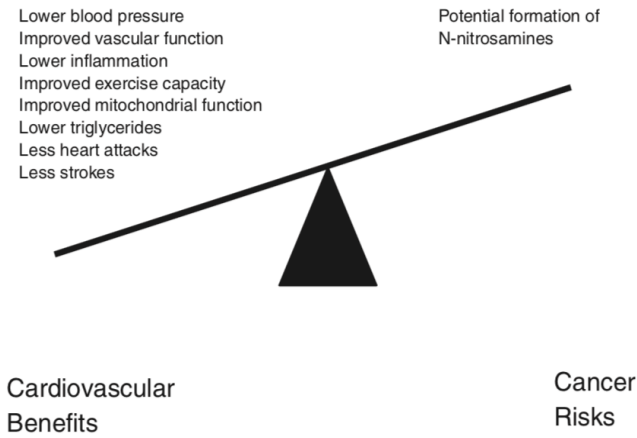


Figure 4. Risk-benefit analysis of nitrite and nitrate (Bryan & Ivy, 2015, p. 650)

Therefore although nutritional decisions are often complex and difficult to parse, the question of nitrates is fairly clear cut. Given the minimal or non-existent risks of methaemoglobinaemia (Mensinga et al., 2003) and N-nitroso carcinogens (Bedale et al., 2016, p. 88), and the ever increasing list of cardiovascular benefits of nitrate consumption (fig. 4), a diet rich in vegetable nitrates appears to be a healthy and safe option. In a world where the best-case scenario is merely a delay in the progression of cardiovascular disease and cancer, nitrate supplementation may be a panacea.

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