# Nitric Oxide and Gastrointestinal Health

The explosion of NO research in recent years has been accompanied by some provocative, brilliant and trend setting findings about this simple molecule. NO plays a critical role in the health of the gut by protecting against various bacterial invaders and by maintaining the integrity of the stomach lining, called the gastric mucosa. The gastric mucosa is a layer of mucous that lines the inside of the stomach, and it essential for protecting the cells of the stomach, and the rest of the body, from the acidic environment within.

The human gastrointestinal tract (GIT) is a long winding tube consisting of various types of cells from the mucosal cells in the mouth to the epithelial cells of the intestines and everything in between. Proper functioning of the GIT is crucial for the maintenance of optimal health. However, the GIT and its cells must constantly cope with a complex assortment of friendly and pathogenic bacteria, yeasts, toxins, chemicals, enzymes and nutrients like fats, carbohydrates, proteins and fiber. Further adding to the enormous complexity of this task is the fact that all of this must take place across a wide range of pH levels, from acidic, to neutral to alkaline.

## Gut Microflora and NO

In terms of cell number, bacterial cells in the GIT outnumber human cells by a staggering 9 times! These bacterial cells encompass many different species and have a wide range of functions – some of them friendly and some of them detrimental. For example, some bacteria in the gut are responsible for the synthesis of certain essential nutrients like B vitamins, vitamin K and folic acid, others are important for facilitating the absorption of nutrients like calcium, and still others produce harmful toxins. Real estate in the GIT is highly sought after, resulting in intense competition between all the different bacteria for nutrients and space. The two key sites with the highest density of the bacterial cells are the mouth and the large intestines.

Maintaining healthy colonies of bacterial flora throughout the GIT is essential for good health. Unfortunately, this delicate balance is easily disturbed by poor diet, an unhealthy lifestyle, the use of certain prescription medications like antibiotics and many other factors.

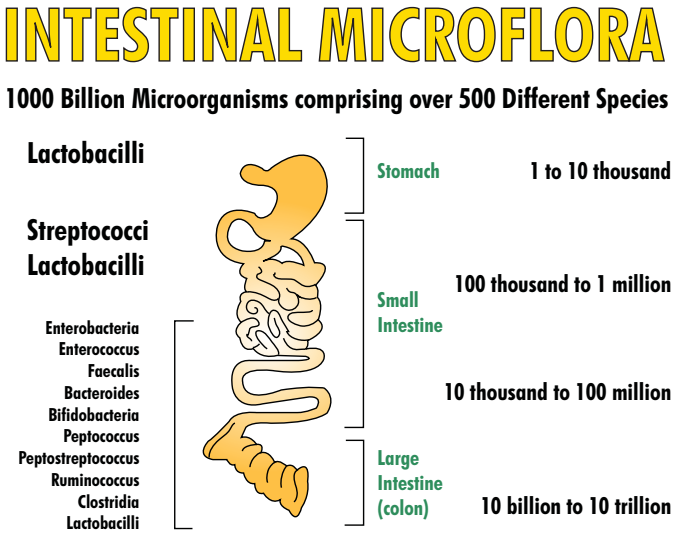



Figure 11. The bacteria or "microflora" of your gastrointestinal tract. A healthy balance of these microorganisms is essential for maintaining good health.

In the mouth, saliva plays a critical role in not only lubricating the food to facilitate swallowing but also in the production of key enzymes that begin the digestive process. Humans produce approximately 1 liter of saliva per day. This salvia is produced in the mouth and eventually makes its way into the stomach. Nitrates obtained from the diet (for example from the consumption of lettuce, beetroot, spinach, leeks etc.) are rapidly converted into nitrite by a specific type of bacteria housed on the surface of the tongue. Spitting or not swallowing the saliva following consumption of the above nitrate rich foods results in a lower nitrite concentrations in the blood; hence the age-old but sensible advice, "eat your greens but don't spit". Similarly, the use of mouthwash also results in lower blood nitrite levels due to the destruction of the bacteria on the tongue. It is therefore advisable not to use mouthwash immediately after eating vegetables, so as not to negate the benefits of these nitrate rich foods. A better strategy would be to drink a cup of green tea after consuming a plate of salad or spinach; this is a healthy alternative that will not destroy these important nitrate reducing bacteria. It is also important to note that the conversion of nitrates into nitrite is enhanced by the presence of certain natural compounds like vitamin C, and antioxidants like the

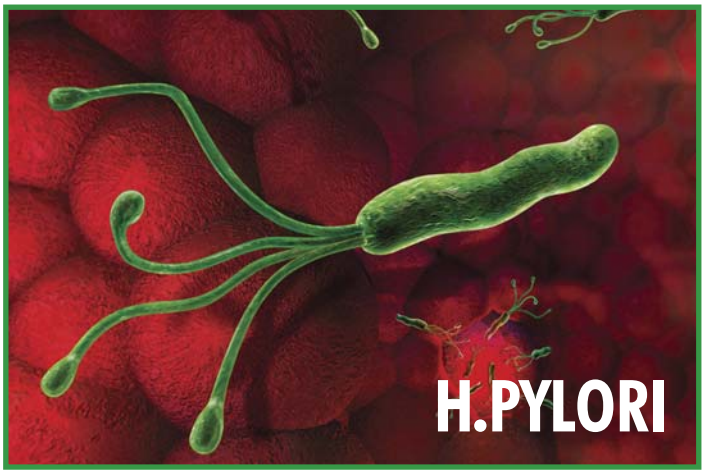
polyphenols present in green tea, pomegranate, grape seed and other many other foods.

The nitrite molecule is actually a negatively charged entity called an anion. In the past, nitrite was considered to be an inert molecule with no biological significance. However, recent research suggests that the nitrite anion acts not only as a precursor to nitric oxide, but also as a suitable storage and transport form for future conversion into NO. This allows NO to be produced in the body where and when it is needed. In addition, and somewhat surprisingly, nitrite and possibly even nitrate have physiological benefits in their own right. For example, in the mouth the nitrite anion has a powerful antimicrobial action that can significantly inhibit certain bacteria like Streptococcus mutans that are well known to contribute to the development of dental cavities. In this way, the actions of the nitrite anion are similar to those of green tea.

As previously mentioned, a rather unique mechanism exists that allows the nitrate we consume to be concentrated in the saliva through the process ofentero-salivary circulation (see Figure 4). In this process, nitrate taken in from a nitrate rich meal is absorbed from the stomach into the blood and is then circulated back into the saliva where nitrate is concentrated and stored. Typically, saliva will have a nitrate concentration that is at least ten-fold higher than the blood and a nitrite content that is one thousand-fold greater than the blood! This helps to explain why animas (and humans) lick their wounds; entero-salivary circulation is a natural means of ensuring that nitrate rich saliva can be converted to nitrite and then into NO for healing! In effect the nitrate in saliva is acting as a pro-drug, meaning that it allows the delivery of NO in an easily useable and transportable form. This is especially important due to the much shorter half-lives (see Box 1) of nitrite and NO.

## NO and the Stomach

The acidic environment of the stomach is deliberately inhospitable and is designed to kill off ingested pathogenic organisms like E. coli, Helicobacter pylori, Pseudomonas aeruginosa, Salmonella enteric, Yersinia, Shigella and others. The extremely low pH of the stomach ensures a direct killing effect of most of these bacteria, helping to prevent harmful infections. However, some bacteria like H. pylori, are resistant to low pH and are able to survive the acidic environment. H .pylori is widely acknowledged to be the causative factor of stomach ulcers, which in turn can lead to the development of gastrointestinal cancer. This bacterial species is particularly resistant to acidic conditions and is very difficult to eliminate once infection occurs. The only known therapy is treatment with a cocktail of powerful antibiotics for periods of 6-8 weeks or longer. Even then the re-infection rate is fairly high. The damaging effects of H. pylori stem from its rather nasty habit of borrowing deep into the gastrointestinal mucosal lining, which over time causes significant damage and ulceration.




The good news is that NO has been shown to help reduce the damage caused by this nasty bacteria. When nitrite rich saliva is swallowed, the high concentration of hydrogen ions in the stomach (the lower the pH the higher the hydrogen ion concentration) react very quickly with the nitrite, reducing it and thus converting it into nitric oxide. The NO then acts locally on the stomach lining and starts the healing process by reducing inflammation in the stomach. This is highly significant since ulceration and ultimately gastric cancer are both inflammatory conditions accompanied by the generation of a large number of damaging free radicals. In addition to its anti-inflammatory and healing effects, NO also increases blood flow to the stomach through its ability to widen blood vessels. By increasing blood flow, NO improves circulation and enhances delivery of nutrients and key immune cells to the site of damage, facilitating and speeding up the healing process. Indeed, gastric NO formation from nitrite and nitrate may act as a first-line defense against swallowed pathogens.

In addition to reducing inflammation of the gastric tissue, the stomach also requires a continuous supply of mucus in order to protect the stomach lining against damage from the acidic stomach contents. NO plays an important role in the maintenance of mucosal integrity by stimulating the production of a protein called mucin, which is a key component of mucous.

## Gastric NO protects against NSAID damage

Most pharmaceuticals like aspirin or non-steroidal anti-inflammatory drugs (NSAID's) have potentially serious side effects including gastric irritation, which can lead to excess bleeding in the stomach and even to the formation of gastric ulcers. This is in part due to the inhibition of protective prostaglandins, a large group of chemicals that protect the gastric mucosa. A number of animal experiments have shown that low NO is associated with a high incidence of gastric irritation. For example, in animals where the NOS enzymes responsible for production of NO were inhibited, there was an increased incidence of ulcers and other gastric side effects. However, when the animals were fed nitrate and then exposed to NSAID's there was significant protective effect, which was attributed to an increased production of specific gastrointestinal protective prostaglandins. These studies suggest that taking your NSAID's or other potentially stomach irritating drugs like aspirin, with foods rich in nitrates is a sensible option. In fact, pharmaceutical companies are on the verge of releasing drug formulations that combine NSAID's and NO donors in order to help reduce the negative impacts these drugs have on the gastrointestinal tract.

When NO Production is Impaired

The NO3-NO2-NO reduction process can become inefficient under various conditions, especially as a result of factors affecting the efficiency and normal functioning of the gastrointestinal tract. For example, the normal cycle of nitrate and nitrite storage and NO production can be impaired in seniors, patients in intensive care, patients on long term antibiotics, patients consuming too many antacids or patients not producing very much energy.

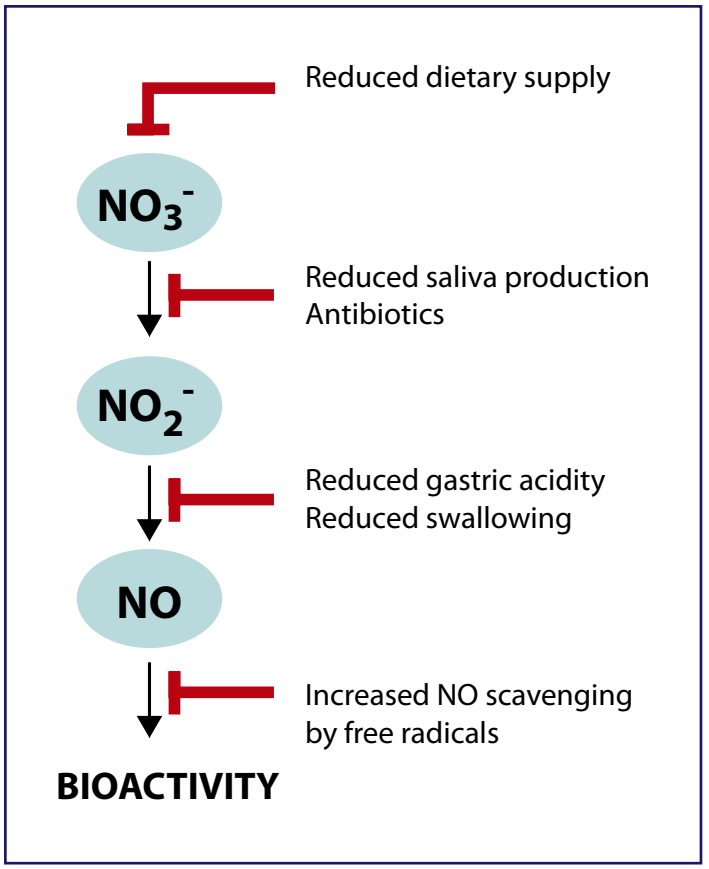



Figure 12. Various factors that can negatively affect the efficiency of the NOx3,2,1 pathway of NO production (from Weitzberg et al., 2010)

Disturbances of the pathway may occur at various levels; for example, reduced saliva production can impair nitrite production, reduced stomach acidity can impair NO production and high levels of free radicals can act to scavenge NO before its beneficial actions are realized. It may be advisable for patients in these conditions to consider an increased consumption of nitrates to help boost NO production.