formation.[66] It is not clear if the reduction in NO production in the stomach is causal for increased incidence of carcinoid tumors. The safety of long-term PPI administration needs serious prospective study. I would strongly suggest that the role of NO be investigated in such studies.

NSAIDS

Prostacyclin (PGI2) is a vasodilator and an inhibitor of platelet aggregation, properties consistent with cardioprotection. More than a decade ago, inhibition of cyclooxygenase-2 (COX-2) by the nonsteroidal anti-inflammatory drugs (NSAIDs) rofecoxib (Vioxx) and celecoxib (Celebrex) was found to reduce the amount of the major metabolite of PGI2 in the urine of healthy volunteers. This suggested that this particular class of NSAIDs might cause adverse cardiovascular events by reducing production of cardioprotective PGI2. This prediction was based on the assumption that the concentration of PGI in urine likely reflected vascular production of PGI2 and that other cardioprotective mediators, especially NO, were not able to compensate for the loss of PGI2. A number of placebo-controlled clinical trials showed that NSAIDs that block COX-2 increase adverse cardiovascular events.[67] In fact, the reason that drugs such as Vioxx and Celebrex were recalled by the FDA was because of concerns of these side effects. Recent basic science data reveal that deletion of COX-2 enzyme in the mouse vasculature reduces excretion of PGI2 in urine and predisposes the animals to both hypertension and thrombosis. Furthermore, vascular disruption of COX-2 depressed expression of endothelial NO synthase and the consequent release and function of NO.[68] Thus, suppression of PGI2 formation resulting from deletion of vascular COX-2 is sufficient to explain the cardiovascular hazard from NSAIDs, which is likely to be augmented by secondary mechanisms such as suppression of NO production. Recognition of a role of NO during COX-2 inhibition opened the door for novel NO-hybrid drugs such as NO-naproxen or NO hybrids of selective COX-2 inhibitors. Conventional reasoning was that if you could provide a source of NO along with the parent drug, one could overcome the cardiovascular complications from such pharmaceuticals. Unfortunately, this strategy has not proved safe and effective as the lead compound, NO-naproxen (naproxcinod), was not approved by the FDA. Early consideration and/or recognition of the effects of COX-2 inhibitors on endogenous NO production may have delayed its entry into the market and prevented many of the adverse events from these drugs. As such all new and existing classes of pharmacological therapies should consider and assess effect on NO production/activity.

Other nonspecific NSAIDs such as aspirin, naproxen, and diclofenac are highly effective drugs that inhibit pain and inflammation; and perhaps due to the role of inflammation in the underlying etiology, the utility of these powerful drugs is limited due to their gastrointestinal (GI) side effects, notably peptic ulceration and GI bleeding.[69] It has been demonstrated that pretreatment with dietary nitrate protects against diclofenac-induced gastric ulcers likely via enhanced nitrite-dependent intragastric NO formation and concomitant stimulation of mucus formation.[70] Although it is not clear if nonspecific NSAIDs are associated with a loss of NO function, it is clear that providing additional NO through nitrate and nitrite ameliorates the damage caused by NSAIDs.

Summary

Everyday lifestyle choices and the advents of modern pharmacology and standard of care negatively affect NO production, activity, and homeostasis. As such, proposed pharmacological therapies should consider NO levels as a safety and long-term efficacy indicator. Increasing awareness of maintaining NO levels through diet, lifestyle, and caution regarding medication is critical for physicians and patients. Medical literature is rich in establishing NO homeostasis as crucial for cardiovascular, neural, and immune health, but this level of correlation is not reflected in modern-day medical practice. This article focused on raising awareness regarding the same. Perhaps the best strategies for overcoming NO deficiencies from lifestyle or pharmacological therapies is through the nitrate-nitrite-NO pathway.[18] This approach is dietary and might be the safest of ways to maintain endothelial health and NO homeostasis in vivo. This simple dietary modification can prevent a number of chronic disease states, including cerebral vasospasm, ischemia-reperfusion injury, sickle cell disease, hypertension, peripheral artery disease, pulmonary hypertension, gastric ulceration, inflammatory bowel disease, hyperlipidemia, and inflammation.[71,72] A more holistic approach to modern-day care, with an emphasis on maintaining NO levels, has future implications in reversing the current trends seen in chronic disease management.

Notes

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