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The role of nitric oxide in inflammation and oxidative stress

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Abstract

Nitric oxide (NO) is one of the most important components of blood vessels' health. NO is a gas compound with different physiological and biochemical effects on the body. It is a free radical, which plays as an endogenous and endothelium relaxing factor. NO has a protective role in digestive system which also plays different roles in the immune system as a mediator of immunity; e.g. regulating immune response, and stimulation and suppression of the immune system. NO has three isoforms each of which is expressed by a special gene. These isoforms include neuronal nitric oxide synthase (nNOS) and endothelial nitric oxide synthase (eNOS) which both are depending on calcium and calmodulin. The third isoform, independent on calcium and calmodulin, is inducible nitric oxide synthase (iNOS). Even in special conditions such as renal ischemia-reperfusion, it has been shown that high iNOS and low eNOS levels are involved in increased inflammation and connective tissue damage.

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Introduction

Nitric oxide (NO) is a gas compound with a short half-life which has different physiological and biochemical effects on the body. NO plays as a messenger molecule in many biological systems. The majority of effects of NO is through producing circular guanosine monophosphate. NO is produced by nitric oxide synthases (NOS) enzyme in the body. NO enzyme has three major isoforms including neural, endothelial, and inductive isoforms (1). In process of producing NO, L-arginine amino acid is used as a substrate. Studies have shown that depending on the type of the producer enzyme, NO can have both apoptotic and anti-apoptotic effects (8). Studies suggest that in hypothyroidism, NOS in tissues is disturbed, because thyroid hormones are involved in NOS therefore in hypothyroidism (9). In this study, the role of NO synthesized by different isoforms of NOS enzyme in the process of inflammation and oxidative stress is investigated by studying various articles of different databases.

Key point

NOS is an enzyme which synthesizes NO and L-arginine citrulline in several stages, and it uses nicotinamide adenine dinucleotide phosphate and other cofactors to facilitate this process. In this study, we reviewed the role of NO synthesized by different isoforms of NOS enzyme in the process of inflammation and oxidative stress.

Materials and Methods

For this mini-review, we searched Scopus, PubMed/Medline, EBSCO, Embase, Web of Science, directory of open access journals (DOAJ) and Google Scholar (1991 to 2019) with keywords of nitric oxide, neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS), inducible nitric oxide synthase (iNOS), inflammation, mediators of immunity, immune system, endothelium relaxing factor, free radical and oxidative stress.

Nitric oxide effects in the body

NO has different effects inside the body; it plays roles in platelet aggregation, cytotoxicity, blood flow, synaptic transmission, and neurotransmitters (2). NO plays a protective role in digestive system (3). As a free radical, NO also plays the role of being as an endogenous and

endothelium relaxing factor (4). In the immune system, NO works as an antibacterial and antiviral compound has a role in stimulation and suppression of the immune system (5). It has different biological roles in female and male genital systems. Some of these roles include ovulation, menstruation, and sperm mobility (6). NO has a role in heart rate, movements of digestive system, and tonus bronchus (7).

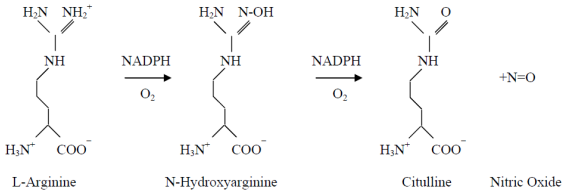

Figure 1. Structure of L-arginine and related molecules.

Nitric oxide synthases enzyme

NOS enzyme is an enzyme which synthesizes NO and L-arginine citrulline in several stages, using nicotinamide adenine dinucleotide phosphate and other cofactors (Figure 1) (10).

In terms of structure, NOS is a homodimeric enzyme and despite its simplicity, has a complex structure (11).

Different isoforms of nitric oxide synthases

NOS has three isoforms each of which is expressed by a special gene. These isoforms include nNOS and eNOS, both depending on calcium and calmodulin. The third isoform which is independent on calcium and calmodulin, is iNOS (12). With the increased concentration of calcium and calmodulin, the probability of connection of iNOS and nNOS to calmodulin is increased and these two produce a higher amount of NO. However, even in very little amounts of calcium, iNOS can connect to calmodulin and production of NO by iNOS takes more time and it creates high concentrations of NO (13). So far, different isoenzymes of NOS have been released among which we can mention sheep brain (14), cow pancreas (15), human platelet (15), and mitochondria of liver cells of rats (15,16). Each of these isoforms has their unique Km and Vmax and even, they may be different from each other in terms of structure and function (16,17).

The role of nitric oxide in inflammation and oxidative stress

NO is an effective free radical in cancers (2). NO can cause a reaction with superoxide and create mediates such as nitrite and nitrogen dioxide which can cause damage to cell DNA. Low levels of NO synthesized by eNOS has pre-cancer effects (18). Depending on conditions and type of cells, NOS plays both inflammatory and anti-inflammatory activities (2). Low levels of NO produced by eNOS can stimulate and regulate pre-inflammatory cytokines, cyclooxygenase 2, and KB nuclear factor (NF-κB) (19). On the other hand, high levels of eNOS in kidney tissue and in the process of renal ischemia-reperfusion can play an important role in reduction of oxidative stress, inflammation, and renal tissue damage. Whereas increased levels of iNOS isoform exacerbate damage and inflammation (20). In 1997, Bédard et al showed that in adjacency of induction tumor necrosis cytokines and interferon gamma, production of NO increases due to increased activity of iNOS. In fact, during this process, increased gene expression of iNOS plays the most important role (21). Studies have shown that using specific inhibitor of iNOS called N6-(1-IminoethyL)-L-Lysine hydrochloride during ischemia-reperfusion induction in kidney tissue of rat decreased renal damage, sodium excretion, and glomerular filtration compared with the rates who had not received the inhibitor (22). In another study, it was showed that rats with low levels of nNOS have long term hippocampus, muscle pain, and nausea (23). On the other hand, decreased eNOS in rats led to blood pressure and unnatural changes in them (24). The rats with low levels of iNOS are more sensitive to inflammatory damages and tumors, but they are more resistant to septic and shock (25). NO formed by eNOS activity plays a role in the prevention of adhesion of leukocytes and platelets to the wall of arteries (26). Studies suggest the effective role of iNOS in inflammation process and exacerbation of inflammation. NO which is synthesized by iNOS plays a role in regulation and increase of cyclooxygenase-2 enzyme (27). Cyclooxygenase-2 enzyme plays an important role in inflammation process during illness and inflammation (28). Studies suggest that during the process of kidney ischemia-reperfusion, inhibition of iNOS by specific inhibitors leads to reduction of inflammation and renal damages. In fact, NO produced by iNOS is effective in inflammation and renal damages during the process of ischemia-reperfusion (29). Studies have shown that immunoglobulin E increases expression of iNOS through reacting with CD-23 and keratinocyte cells (30). Moreover, evidence shows that during inflammation, asthma, and stimulation of the immune system, the amount of iNOS increases (31). Synthesis of high levels of NO which is mainly done by iNOS plays pre-inflammatory roles (32). Whereas increased nNOS can be effective in making the arteries and respiratory muscles loose and improve respiration (33). Studies suggest that increased inflammation and renal damages are caused by decreased activity of eNOS during ischemia-reperfusion (34). Additionally, studies have indicated that gene expression of eNOS is effective in apoptosis stimulation and decreased movement and invasion of cancer cells (35). It has been suggested that the activity of eNOS is very important in the inhibition of reactive oxygen species; therefore, it has a role similar to that of superoxide dismutase enzyme (36).

Studies indicate different roles of NO in inflammation process for which inhibiting drugs can be effective in treating and controlling the diseases. Glucocorticoids

specifically inhibit expression of iNOS. Specific inhibitors of iNOS such as alkaloids were being investigated suggesting that they are promising factors to inhibit inflammatory response systematic syndrome (37). Studies have shown that expression of iNOS increases the incidence of infections, therefore, using glucocorticoid steroids can be effective in reduction of the effects of infection through inhibition (38). In a previous study, the effects of anthocyanins on iNOS and eNOS were investigated where they showed that increased eNOS plays a role in homeostasis of coronary arteries, while increased iNOS raises the probability of heart diseases (39). There is evidence suggesting the role of eNOS on energy production and using fatty acids by muscles (40). High level of reactive oxygen species leads to oxidative stress. Studies have indicated that eNOS plays a role in preservation of balance between reactive oxygen species and antioxidants (41). Nuclear factor kappa light chain enhancer of activated B cells (NF-Kb) causes iNOS synthesis and this condition leads to edema and hyperalgesia (42). Studies suggest that isoforms of eNOS and nNOS always exist in low levels but in activated status while iNOS isoform increases in case of inflammation and in response to inflammatory cytokines and lipopolysaccharides (43). The amount of iNOS increases in response to interleukins and tumor necrosis factor-α (44). In pathologic conditions, the amount of NO produced by iNOS is increased and it can reveal neurotoxic characteristics (45). NO produced by iNOS and nNOS plays a role in activation of cyclooxygenase and inflammatory response, particularly neural inflammation by nNOS (46). Evidence suggests that in pathologic conditions, there is a key relationship between cyclooxygenase and iNOS enzyme. During inflammation, iNOS increases the amount of cyclooxygenase-2 and as a result, it leads to increased effects of cytotoxic (47). Studies have shown that using iNOS inhibitor leads to decreased production of prostaglandin E (48). Additionally, studies revealed that stress condition cause changes in structure of endothelial cells and finally, it leads to increased activity of eNOS (49). In general, factors such as cyclooxygenase, lipopolysaccharide, tumor necrosis factor-α, interferon-γ, interleukin-1β play a role in increased activity of iNOS (50). Overall, nNOS is mainly involved in neural tissue while iNOS and eNOS are both mainly involved in inflammation and immune system, and in blood pressure regulation, respectively (51).

Conclusion

In general, it can be stated that two forms of nNOS and eNOS are constantly and continuously produced in low levels by relevant cells. However, iNOS is of inductive type and it plays a significant role in immunity and inflammation process. This isoform increased in inflammation condition and it exacerbates inflammatory effects. Even in special conditions such as renal ischemia-reperfusion, high levels of iNOS but low levels of eNOS are involved in increased inflammation and tissue damage.

Authors' contribution

SP searched the data and prepared the primary draft. FA and AH edited and finalized the manuscript. All authors read and signed the final manuscript.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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