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Nitric Oxide: Structure, Pathophysiology and Clinical Significance

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ABSTRACT: Hypertension is the most important modifiable risk factor and, if treated, leads to a reduction in cardiovascular diseases and mortality. A recent perspective emphasizes the central role of nitric oxide bioavailability in the maintenance of healthy vasculature and the regulation of blood pressure. The molecule nitric oxide is very complex with far-reaching implications concerning cardiovascular well-being and pathology. Synthesis of nitric oxide as well as signaling cascades and their regulation thus stands as a critical process in acquiring an understanding regarding its involvement under physiological as well as pathological conditions. With the rapid pace at which NO research is evolving, there are significant gaps in our knowledge that must be filled in if we are ever to take full advantage of its therapeutic potential. Nitric oxide is also considered to be a very important molecule involved in the defense of hypertension through its effects on endothelial function and vascular homeostasis. This review will summarize the current state of knowledge regarding the relationship between NO and hypertension and will attempt to identify those areas where significant lacunae exist and where further research would be appropriate. In addition, focus is directed toward the structure and clinical relevance of NO, describing its functions in endothelial activity, cardiovascular health, and any possible clinical utility.

INTRODUCTION

Nitric oxide (NO) is now known to be an important, if not the most important, signaling molecule produced in the vascular system, with a wide range of biological activities performed in different systems. Regular generation of NO within the endothelial cells "is essential for the maintenance of vasculature homeostasis as well as normal endothelial function" (Tousoulis et al., 2012). This review represents up-to-date research results on the relationship of NO with hypertension and specifies further directions of filling this question. It concentrates on the construction and clinical manifestation of NO, explaining its place on the territory of endothelial function, cardiovascular, and possible therapeutic effects.

BASIC STRUCTURE OF NO

Nitric Oxide (NO) is a small molecule gas with a simple diatomic structure, although its biological actions are profound. Nitric oxide synthase exists in three isoforms: endothelial, neuronal, and inducible. Whereas eNOS and nNOS are expressed constitutively and in iNOS conditions of their dependence on calcium/calmodulin for activation, iNOS is generally up-regulated in response to inflammatory stimuli to produce NO in much larger amounts. These enzymes are very important in the context of vaso-regulation and protection against oxidative stress (Farah et al., 2018).

Another route of NO- synthesis, apart from enzymatic production, arises from the nonenzymatic synthesis of NO from different precursors particularly under hypoxic conditions the importance of NO in exercise In additon to enzymatic generation of NO, an alternative source of NO involved nonenzymatic pathways, which include precursors other than those involved in enzymatic synthesis when these are particularly relevant under hypoxic conditions (Tejero et al., 2019). The importance of NO in exercise has been underscored by the fact that other precursory pathways of NO synthesis, such as the ones involved in nonenzymatic synthesis, are upregulated in exercise to increase the bioavailability of NO and induce vasodilation (Nystoriak & Bhatnagar, 2018).

ROLE OF NITRIC OXIDE IN CARDIOVASCULAR HEALTH

NO has been traditionally well recognized as a vasodilator factor important in the control of blood flow and blood pressure. NO reacts with the vascular smooth muscle cells inducing a particular level of relaxation of the smooth muscles which is essentially required against the development of hypertension and cardiovascular pathologies associated with it (Martínez-Ruíz et al., 2011).

Moreover, NO participates in antiplatelet and antiadhesive actions on leukocytes, providing protective effects against atherogenesis (Oesterle et al., 2017).

Research has indicated that dietary nitrates in green leaves and beetroot can increase the production of NO through the nitrated-nitrite-NO pathway, thus offering a dietary means of optimizing cardiovascular health (Lidder & Webb, 2013). The compound resveratrol antioxidant characteristic has also been associated with the maintenance of NO signaling, not allowing the superoxide to generate from eNOS detached to further underline the interplay amongst diet, NO availability, and oxidative stress (Lundberg et al., 2015; Xia et al., 2017).

Nitric oxide mostly synthesized by endothelial NO synthase is really important for vasodilation and the preservation of vascular homeostasis. eNOS is crucial for endothelial-dependent reactions that dominate over the control of blood pressure and other mechanisms associated with vasoprotection (Förstermann & Sessa, 2012). Pathological states especially entail a deficiency of produced NO resulting in huge imbalances within the endothelium that highly contribute to hypertension pathogenesis (Tousoulis et al., 2012).

The bioavailability of NO depends on several factors, one of them being the expression of eNOS and its cofactors. In conditions with reduced levels of cofactors of eNOS, the enzyme might get uncoupled to produce superoxide instead of NO (Farah et al., 2018), Uncoupling further enhances oxidative stress, impairing endothelial function even more, and tends to stiffness of the arteries-hallmarks of hypertension (Gallo et al., 2022).

Endothelial dysfunction is the central issue in hypertension and is associated with an increased cardiovascular risk. There is evidence that exocytosis of extracellular vesicles could carry antihypertensive factors into the circulation, thus new therapeutic avenues. Further, vitamin D has been shown to be a regulator of eNOS, which is an indicator that even lifestyle factors can interfere with NO availability in the regulation of blood pressure.

The aging process poses yet another challenge since it is related to reduced bioavailability of NO, in view of eNOS dysfunction. This dysfunction leads to vascular remodeling and enhanced infiltration of leukocytes; two factors may further compound hypertensio (Gallo et al., 2022).

PATHOPHYSIOLOGICAL IMPLICATIONS OF NITRIC OXIDE

Though, NO is implicated in the pathogenesis of a number of disease conditions in view of its beneficial role in the maintenance of homeostasis. The overproduction of NO especially from iNOS in the course of inflammatory responses has been linked to tissue damage and chronic inflammatory diseases. On the other hand, reduced availability of NO results in endothelial dysfunction which is the earliest change in a number of cardiovascular diseases like atherosclerosis, hypertension, and heart failure.

Fractional exhaled NO is now measured, a non-invasive biomarker in the evaluation of airway inflammation, especially in pathologies such as asthma— thus extending the frontiers of NO's roles past the cardiovascular system (Hamblin, 2018). NO has dual roles as a signaling molecule and, depending on conditions, as a possible mediator of damage, indicating the complexity of pathophysiological implications of NO.

Several studies suggest that the bioavailability of NO can be increased by specific interventions. For example, an intervention that increases the vascular levels of tetrahydrobiopterin would need to be shown first to increase NH availability, a key player in cardiovascular health (Galiè et al., 2019). Furthermore, arginine supplementation improved endothelial function and vascular tone in hypertensive humans (Bendall et al., 2014).

A noteworthy player in this game of oxidants and NO production. Increased oxidants in hypertensive states contribute to vascular iNOS might produce NO pathology exogenously abundant, pathologically speaking (Carnicer et al., 2013), and therefore vascular dysfunction. Therapeutically, this duality muddies the landscape of, implying that while NO is beneficial, its dysregulation can have adverse effects.

Given the importance of NO in hypertension, interest in therapeutic approaches aimed at enhancing NO signaling is high. Both targeted modulation of eNOS activity and the administration of NO precursors or enhancers can reverse oxidative stress and restore endothelial function. Another supplement that is gaining ground as a possible intervention is folic acid, which by promoting eNOS coupling and superoxide radical scavenging, increases NO bioavailability.

Although these advances exist, several important knowledge gaps remain. For example, the exact mechanisms by which the various interventions modulate eNOS activity and NO bioavailability in different patient populations need to be further clarified. Long-term safety and efficacy of supplementation of hypertensive patients with arginine and folic acid is not well rigorous investigated.

CONCLUSIONS

Nitric oxide is a double-edged molecule of cardinal importance with the cardiovascular system and its pathologies. Therefore, the synthesis, signaling pathways, and regulatory mechanisms of this molecule have become part of the strategic pursuit toward understanding roles of NO in both physiology and pathology. The more intricate faces of NO underlie just how far-fetched the existing knowledge gaps must be addressed to fully exploit its therapeutic potential. Nitric oxide is also involved in protecting the body against the development of hypertension through actions on endothelial function and vascular homeostasis. Although it appears

from current investigations that the involvement of NO in hypertension pathogenesis, as well as possible strategies for control, is now understood, this paper hereby gaps the notes and identifies the research left undone to date on this issue. The third element about hypertensive management is the complicated relationship that exists between NO, eNOS, and the health of the blood vessels.

REFERENCES

1) Andrukhova, O.., Slavic, S.., Zeitz, Ute., Riesen, S.., Heppelmann, M. S.., Ambrisko, T.., Markovic, Mato., Kuebler, W.., & Erben, R.. (2014). Vitamin D is a regulator of endothelial nitric oxide synthase and arterial stiffness in mice.. *Molecular endocrinology* , 28 1 , 53-64 . http://doi.org/10.1210/me.2013-1252
2) Bendall, J.., Douglas, G.., McNeill, E.., Channon, K.., & Crabtree, M.. (2014). Tetrahydrobiopterin in cardiovascular health and disease.. *Antioxidants & redox signaling* , 20 18 , 3040-77 . http://doi.org/10.1089/ars.2013.5566
3) Carnicer, R.., Crabtree, M.., Sivakumaran, V.., Casadei, B.., & Kass, D.. (2013). Nitric oxide synthases in heart failure.. *Antioxidants & redox signaling* , 18 9 , 1078-99 . http://doi.org/10.1089/ars.2012.4824
4) Cinelli, Maris A.., Do, H.., Miley, Galen P.., & Silverman, R.. (2020). Inducible nitric oxide synthase: Regulation, structure, and inhibition. *Medicinal Research Reviews* , 40 , 158 - 189 . http://doi.org/10.1002/med.21599
5) Farah, C.., Michel, L.., & Balligand, J.. (2018). Nitric oxide signalling in cardiovascular health and disease. *Nature Reviews Cardiology* , 15 , 292-316 . http://doi.org/10.1038/nrcardio.2017.224
6) Förstermann, U.., & Sessa, W.. (2012). Nitric oxide synthases: regulation and function.. *European heart journal* , 33 7 , 829-37, 837a-837d . http://doi.org/10.1093/eurheartj/ehr304
7) Galiè, N.., Channick, R.., Frantz, R.., Grünig, E.., Jing, Z.., Moiseeva, O.., Preston, I.., Pulido, T.., Safdar, Z.., Tamura, Yuichi., & McLaughlin, V.. (2019). Risk stratification and medical therapy of pulmonary arterial hypertension. *The European Respiratory Journal* , 53 . http://doi.org/10.1183/13993003.01889-2018
8) Gallo, G.., Volpe, M.., & Savoia, C.. (2022). Endothelial Dysfunction in Hypertension: Current Concepts and Clinical Implications. *Frontiers in Medicine* , 8 . http://doi.org/10.3389/fmed.2021.798958
9) Gambardella, J.., Khondkar, Wafiq., Morelli, M.., Wang, Xujun., Santulli, G.., & Trimarco, V.. (2020). Arginine and Endothelial Function. *Biomedicines* , 8 . http://doi.org/10.3390/biomedicines8080277
10) Hamblin, Michael R. (2018). Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation. *Photochemistry and Photobiology* , 94 . http://doi.org/10.1111/php.12864
11) Kuhn, V.., Diederich, L.., Keller, T. C.., Kramer, Christian M.., Lückstädt, Wiebke., Panknin, C.., Suvorava, T.., Isakson, B.., Kelm, M.., & Cortese-Krott, M.. (2017). Red Blood Cell Function and Dysfunction: Redox Regulation, Nitric Oxide Metabolism, Anemia. *Antioxidants & Redox Signaling* , 26 , 718 - 742 . http://doi.org/10.1089/ars.2016.6954
12) Li, Qiang., Youn, J.., & Cai, H.. (2015). Mechanisms and consequences of endothelial nitric oxide synthase dysfunction in hypertension.. *Journal of hypertension* , 33 6 , 1128-36 . http://doi.org/10.1097/HJH.0000000000000587
13) Lidder, S.., & Webb, A.. (2013). Vascular effects of dietary nitrate (as found in green leafy vegetables and beetroot) via the nitrate-nitrite-nitric oxide pathway.. *British journal of clinical pharmacology*, 75 3, 677-96. http://doi.org/10.1111/j.1365-2125.2012.04420.x
14) Lundberg, J.., Gladwin, M.., & Weitzberg, E.. (2015). Strategies to increase nitric oxide signalling in cardiovascular disease. *Nature Reviews Drug Discovery*, 14 , 623-641 . http://doi.org/10.1038/nrd4623
15) Martínez-Ruíz, A.., Cadenas, S.., & Lamas, S. (2011). Nitric oxide signaling: classical, less classical, and nonclassical mechanisms. *Free radical biology & medicine*, 51 1 , 17-29 . http://doi.org/10.1016/j.freeradbiomed.2011.04.010
16) Nystoriak, Matthew A.., & Bhatnagar, A.. (2018). Cardiovascular Effects and Benefits of Exercise. *Frontiers in Cardiovascular Medicine* , 5 . http://doi.org/10.3389/fcvm.2018.00135
17) Oesterle, A.., Laufs, U.., & Liao, J.. (2017). Pleiotropic Effects of Statins on the Cardiovascular System. *Circulation Research*, 120 , 229–243 . http://doi.org/10.1161/CIRCRESAHA.116.308537
18) Tejero, J.., Shiva, S.., & Gladwin, M.. (2019). Sources of Vascular Nitric Oxide and Reactive Oxygen Species and Their Regulation. *Physiological reviews* , 99 1 , 311-379 . http://doi.org/10.1152/physrev.00036.2017
19) Tousoulis, D.., Kampoli, A.., Tentolouris, C.., Papageorgiou, N.., & Stefanadis, C.. (2012). The role of nitric oxide on endothelial function. *Current vascular pharmacology*, 10 1 , 4-18 . http://doi.org/10.2174/157016112798829760
20) Xia, N.., Daiber, A.., Förstermann, U.., & Li, Huige. (2017). Antioxidant effects of resveratrol in the cardiovascular system. *British Journal of Pharmacology*, 174, 1633 - 1646 . http://doi.org/10.1111/bph.13492