A Mathematical Model for the Role of N_2O_3 in Enhancing Nitric Oxide Following Nitrite Infusion

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Poster Available

Abstract

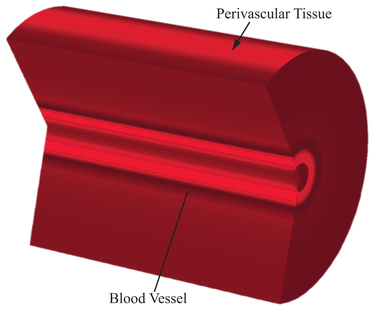
- We developed a mathematical model to investigate the paradoxical effectiveness of nitrite infusion into the bloodstream in eliciting hypoxic vasodilation through nitric oxide (NO) release despite strong hemoglobin scavenging.
- Our model for an arteriole and surrounding tissue examines the hypothesis that dinitrogen trioxide (N_2O_3) is generated during deoxyhemoglobin nitrite reduction and acts as a stable intermediate for preserving NO.

Background

Nitrite has been shown to be a storage pool for NO that is nonproductive at normoxia, but produces NO under hypoxia. The nitrite reductase activity of deoxygenated hemoglobin (deoxyHb) on nitrite infused into the blood has been shown to cause significant vasodilation during hypoxia. A major challenge remains to explain how NO escapes the highly effective trap environment of the erythrocyte after nitrite reduction.[1]

It has been hypothesized that a stable intermediate species – N_2O_3 – is generated during the nitrite-hemoglobin reaction which diffuses away from the erythrocyte and releases NO in tissue.[2] Previous mathematical models have not simulated an NO preservation mechanism and have predicted ineffective NO elevation from blood nitrite reduction.

Model Development

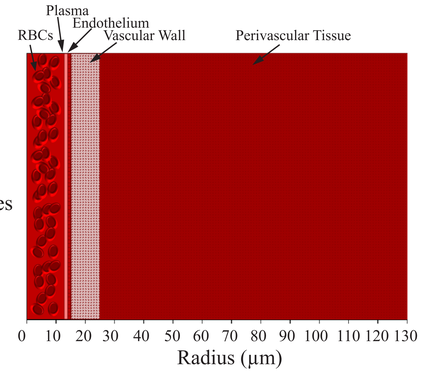


Microcirculatory arteriole and surrounding tissue

Finite element modeling with COMSOL v5.2

Mass transport in steady-state cylindrical coordinates

$$0 = D_i\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C_i}{\partial r}\right)\right] - v_z\frac{\partial C_i}{\partial z} \pm \sum R_i$$



Nitric Oxide

- RBC and tissue scavenging
- eNOS production

$$R_{NO} = R_{NO_{max}}\left(\frac{P_{O_2}}{P_{O_2}+K_m}\right)\left(\frac{\tau_w}{\tau_{ref}}\right)$$

Oxygen

- NO-inhibited tissue respiration[3]

$$R_{O_2} = R_{O_2 max}\frac{P_{O_2}}{P_{O_2}+AppK_m}$$

$$AppK_m = K_m^*\left(1+\frac{C_{NO}}{27\ nM}\right)$$

Nitrite Reductase

- Modified Monod-Wyman-Changeux allostery model[4]

$$k_N = \frac{\left(1+\frac{P_{O_2}}{K_R}\right)^3 k_R + L\left(1+\frac{cP_{O_2}}{K_R}\right)^3 k_T}{\left(1+\frac{P_{O_2}}{K_R}\right)^4 + L\left(1+\frac{cP_{O_2}}{K_R}\right)^4}$$

N_2O_3 Pathway

$$NO_2^- + deoxyHb \xrightarrow{k_N} NO + MetHb$$

$$[MetHb - NO_2^- \leftrightarrow Hb - NO_2] \xleftrightarrow{K_d} MetHb + NO_2^-$$

$$[MetHb - NO_2^- \leftrightarrow Hb - NO_2] + NO \xrightarrow{k_{N_2O_3}} N_2O_3 + deoxyHb$$

$$N_2O_3 \xrightarrow{k_k} NO + NO_2$$

Results

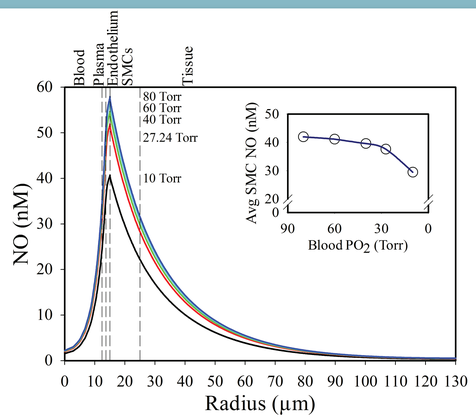


Figure 1: No N_2O_3 pathway, NO concentration profiles for various blood PO_2 concentrations. (Inset) Average NO in SMC region ($15 < r < 25$ μm).

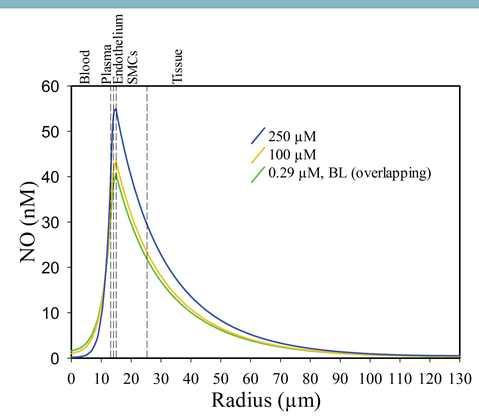


Figure 2: With N_2O_3 pathway, effect of blood nitrite infusions at blood PO_2 = 10 Torr.

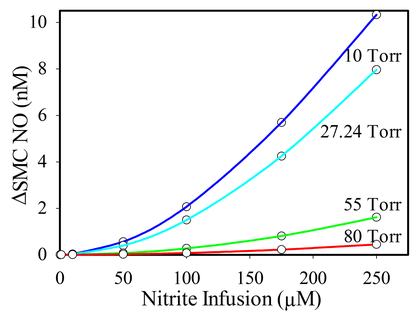


Figure 3: With N_2O_3 pathway, effect of nitrite infusions on SMC NO at various blood PO_2.

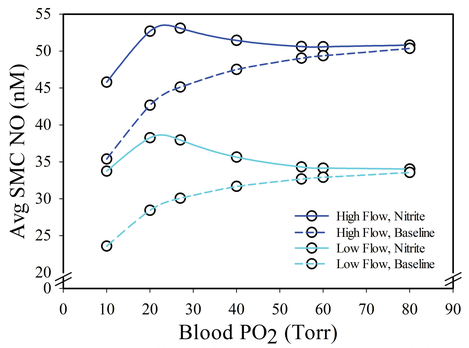


Figure 4: With N_2O_3 pathway, effect of flow changes and 250 μM nitrite on SMC NO.

Discussion

Without the N_2O_3 pathway, our model predicts that nitrite infusion into the blood has little effect on smooth muscle cell (SMC) NO. With the N_2O_3 pathway, moderate infusion levels (>100 μM) can produce a significant rise (~5 nM) in vascular wall NO under moderate to severe hypoxia, consistent at different flow rates. N_2O_3 is produced in the blood and diffuses from the RBCs to the endothelium and tissue, where it rapidly homolyzes to elevate SMC NO.[5]

Some studies have shown that low levels of nitrite and mild hypoxia are sufficient to cause vasodilation, which is not fully explained by our model.[6,7] These results could be explained by the presence of other active nitrite reduction mechanisms, an area of future study.

Conclusions

- With both hypoxia and moderate nitrite infusion, the N_2O_3 pathway can significantly preserve NO produced by blood infusions of nitrite.
- This effect increases as hypoxia and nitrite concentration increases, peaking at the lowest blood PO_2.
- This nitric oxide enhancing mechanism is consistent at different blood flow rates.
- This model does not fully explain how low nitrite levels can still elicit vasodilation in vivo; more detailed modeling of secondary N_2O_3 pathways are required.

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Selected References

1. Gladwin, Mark T., and Daniel B. Kim-Shapiro. "The functional nitrite reductase activity of the heme-globins." Blood 112.7 (2008): 2636-2647.
2. Basu, Swati, et al. "Catalytic generation of N2O3 by the concerted nitrite reductase and anhydrase activity of hemoglobin." Nature chemical biology 3.12 (2007): 785-794.
3. Buerk, Donald G., Kenneth A. Barbee, and Dov Jaron. "Modeling O2-dependent effects of nitrite reductase activity in blood and tissue on coupled NO and O2 transport around arterioles." Oxygen Transport to Tissue XXXII. Springer US, 2011. 271-276.
4. Rong, Zimei, Michael T. Wilson, and Chris E. Cooper. "A model for the nitric oxide producing nitrite reductase activity of hemoglobin as a function of oxygen saturation." Nitric oxide 33 (2013): 74-80.
5. Liu, Yien, et al. "A mathematical model for the role of N2O3 in enhancing nitric oxide bioavailability following nitrite infusion." Nitric Oxide 60 (2016): 1-9.
6. Dejam, André, et al. "Nitrite Infusion in Humans and Nonhuman Primates Endocrine Effects, Pharmacokinetics, and Tolerance Formation." Circulation 116.16 (2007): 1821-1831.
7. Cosby, Kenyatta, et al. "Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation." Nature medicine 9.12 (2003): 1498-1505.

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