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$_2$O$_3$) is generated during deoxyhemoglobin nitrite reduction and acts as a stable intermediate for preserving NO.

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 deoxygynated 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. It has been hypothesized that a stable intermediate species – N$_2$O$_3$ – is generated during the nitrite-hemoglobin reaction which diffuses away from the erythrocyte and releases NO in tissue. Previous mathematical models have not simulated an NO preservation mechanism and have predicted ineffective NO elevation from blood nitrite reduction.

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Model Development

Mass transport in steady-state cylindrical coordinates

\[ 0 = D_r \left( \frac{\partial}{\partial \rho} \left( \rho \frac{\partial C}{\partial \rho} \right) \right) - \frac{\partial C}{\partial z} + \sum R_i \]

Nitric Oxide

• RBC and tissue scavenging
• eNOS production

\[ R_{NO} = R_{NO,scav} \left( \frac{P_{NO}}{P_{NO} + K_{NO}} \right) \]

Oxygen

• NO-inhibited tissue respiration\(^1\)

\[ R_{O_2} = R_{O_2,scav} \left( \frac{P_{O_2}}{P_{O_2} + K_{O_2}} \right) \]

\[ AppK_{NO} = K_{NO} \left( 1 + \frac{C_{NO}}{23 nM} \right) \]

Nitrite Reductase

• Modified Monod-Wyman-Changeux allosteric model\(^2\)

\[ K_a = \frac{1 + \frac{P_{NO}}{K_{NO}}}{1 + \frac{P_{NO}}{K_{NO}}} \]

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N$_2$O$_3$ Pathway

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Results

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Discussion

Without the N$_2$O$_3$ 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$_2$O$_3$ is produced in the blood and diffuses from the RBCs to the endothelium and tissue, where it rapidly homologizes to elevate SMC NO.

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. 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$_2$O$_3$ 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$_2$O$_3$ pathways are required.

Selected References


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Poster Available

Supported by NIH U01 HL 116256