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Just Sit Back and Relax with Sodium Nitroprusside

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Abbreviations:
DHR: dihydrorhodamine-123 DHR
DDT: dithiothreitol

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Abstract:

Sodium nitroprusside (SNP) is used clinically as an antihypertensive agent. SNP's ability to generate nitric oxide ($NO^{\bullet}$) makes it a powerful vasodilator in treating hypertension and severe cardiac failure. The generation of nitric oxide activates guanylated cyclase and forms cGMP, the second messenger that will relax smooth muscle. Fatalities to SNP administration can occur. Large amounts of SNP infused at high rates can produce cyanide [7]. SNP is metabolized to cyanide and then to thiocyanate, thiocyanate is then be excreted by the kidneys. SNP can be used as an alterative to nitroglycerin in the treatment of hypertenision.

Introduction

Sodium nitroprusside (SNP) is used clinically as an antihypertensive agent. SNP's ability to generate nitric oxide ($NO^{\bullet}$) makes it a powerful vasodilator in treating hypertension and severe cardiac failure [1, 2]. Nitroprusside is able to dilate arterial and venous vessels to increase venous return while reducing peripheral vascular resistance. The generation of nitric oxide activates guanylated cyclase and forms cGMP, the second messenger that will relax smooth muscle (Figure 1).

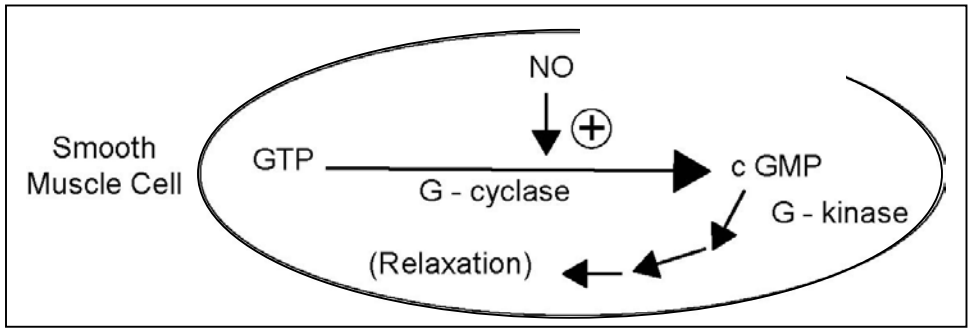

Figure 1. Schematic of the reaction of smooth muscle cells to NO. The generation of NO activates and forms cGMP, which will cause the relaxation of the muscle.

The decrease in blood pressure is due to a decrease in vascular resistance while cardiac output is constant [2]. SNP is known to be light sensitive, the generation of nitric oxide is due to the photolytic decomposition [3]. To liberate the nitrosonium ligand SNP must interact with a reducing agent such as a thiol like ascorbate [4]. Extreme caution must be used when administering SNP because it can produce toxic levels of cyanide.

Characteristics of Sodium Nitroprusside

SNP is a metal nitrosyl complex made up of iron, cyanide groups, and a nitro moiety [$\mathbf{Na_2Fe(CN)_5NO}$] (Figure 2) [2].

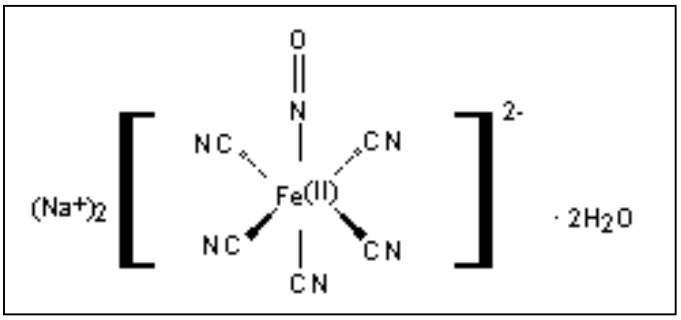

Figure 2. Structure of sodium Nitroprusside.

It was discovered that SNP was light sensitive and when exposed would have an electronic structural change. The change observed for SNP was a metal-to-ligand charge transfer [5]. When exposed to irradiation with blue-green light a long-lived metastable state was produced. Two metastable states (SI and SII) can be formed and fall between the light spectral range of 350-580 nm at temperatures below 200 K [6]. Both states can be reversibly transferred back to ground state when exposed to irradiation with light in the red spectral range of 632 nm [6]. It is believed that the main molecular axis of N-C-Fe-N-O remains unchanged but that the NO group becomes inverted creating a isonitrosyl structure [6]. The π*NO orbital is energetically low lying empty positioned between the completely filled Fe($3d_{xy,yz,}$ $3d_{xy}$) and the empty Fe($3d_{x^2-y^2}$,$3d_{z^2}$), then a metal-to-ligand charge transfer occurs in a two-step process. The diamagnetic ground state shift to a higher energy in the SI and SII state, which is just long enough for a rearrangement of the rest-electron density on the iron central atom (reaction 1) [5].

Fe($3d_{xy,yz,}$ $3d_{xy}$)→ π*NO⇒SI, SII **reaction 1**

The physical background for the different states are still under investigation but the above information shows a start at a possible structural rearrangement [5].

Reactions during Nitric Oxide Production

Sodium nitroprusside has the ability to produce nitric oxide, which leads to the relaxation of the smooth muscle. The true mechanism by which SNP generates the nitric oxide is still being investigated [3]. It is thought that the photolytic decomposition could play a key role in the generation of nitric oxide (Reaction 2) [3].

$$[Fe(CN)_5NO]^{2-} + H_2O \rightarrow [Fe(CN)_5H_2O]^{2-} + NO \qquad \textbf{Reaction 2}$$

A 1:1 molar ratio of nitric oxide and the by-product pentacyanoferrate complex occurs with this reaction generally *in vitro*. An alterative pathway that can lead to the liberation of the nitrosonium ligand is through the reaction with reducing agents such as thiols. Ascorbate is a key player in the reductive decomposition of SNP. The initial step requires a nucleophilic addition of thiolate on the nitrogen atom (Reaction 3) [3].

$$[Fe(CN)_5NO]^{2-} + RS^- \rightarrow [Fe(CN)_5N(O)SR]^{3-} \qquad \textbf{Reaction 3}$$

The adduct that formed will decompose to $[Fe(CN)_5NO]^{3-}$ and the disulfide followed by a reversible dissociation of cyanide ligand (Reaction 4 and 5).

$$[Fe(CN)_5N(O)SR]^{3-} \rightarrow [Fe(CN)_5NO]^{3-} + 1/2RSSR \qquad \textbf{Reaction 4}$$

$$[Fe(CN)_5NO]^{3-} \leftrightarrow [Fe(CN)_4NO]^{2-} + CN^- \qquad \textbf{Reaction 5}$$

The environmental conditions will determine the fate of the final products. If the conditions are in favor of re-oxidation then the intermediates can reform SNP. In the presence of oxygen a cycling of SNP can occur producing superoxide, resulting in the consumption of thiolate (Reaction 6, 7) [3]. This reaction occurs in microsomes, and has been observed in the forming hydroxyl radical as well

$$[Fe^{2+}(CN)_4NO]^{2-} + CN^- + O_2 \rightarrow [Fe^{3+}(CN)_5NO]^{2-} + O_2^{\bullet-} \qquad \textbf{Reaction 6}$$

$$[Fe^{2+}(CN)_5NO]^{3-} + O_2 \rightarrow [Fe^{3+}(CN)_5NO]^{2-} + O_2^{\bullet-} \quad \textbf{Reaction 7}$$

The superoxide formation bring up the question would nitric oxide react with the superoxide to form peroxynitrite [3]. To determine if this reaction can occur dithiothreitol (DDT) was used to reduce SNP and examine the rate of oxidation of dihydrorhodamine-123 (DHR). The results from some studies agreed with the formation of either peroxynitrite or hydroxyl radicals (Figure 3).

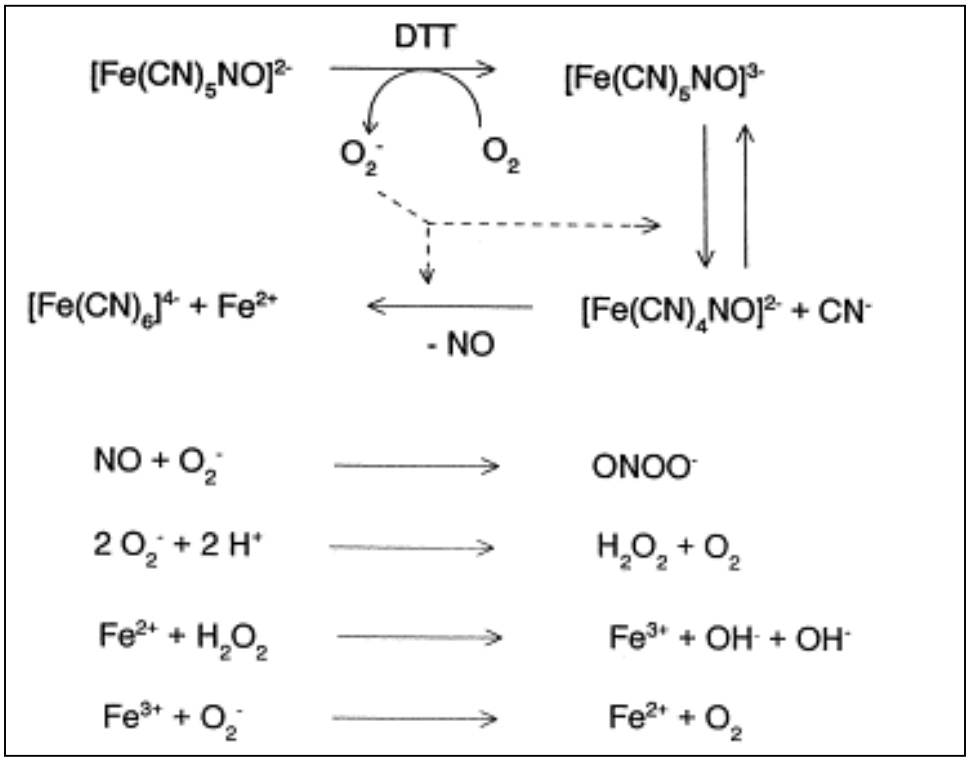

Figure 3 Formation of oxygen-derived free radicals and peroxynitrite during DTT-mediated reduction of SNP. This schematic proposes the sites of action of superoxide on the decomposition of intermediates [3].

The formation of peroxynitrite in this study resulted from the reaction of nitric oxide and superoxide. The formation of the peroxynitrite under specific conditions may result from the reductive decomposition of SNP [3].

Another study believes that the production of nitric oxide comes from several reduction sequences [4]. The first step is a one-electron reduction, which forms a NP nitroxide radical anion. The radical can then go on to react with oxygen to form superoxide, the NP could then go back to cycle again. Through this study it suggested that NP radical anion could cycle to form superoxide.

Toxic Effects of Sodium Nitroprusside

Fatalities to SNP administration can occur. Large amounts of SNP infused at high rates can produce cyanide [7]. SNP is metabolized to cyanide and then to thiocyanate, thiocyanate is then be excreted by the kidneys. The metabolism of SNP converted in the erythrocytes. Thiocyanate is generated in the liver by an enzyme called rhodanase in the presence of thiosulphate. Thiocyanate toxicity can become life threatening if it is 3-4 times the higher than normal. Thiocyanate will inhibit both the uptake and binding of iodide. When administering SNP the generation of cyanide ion could be more than the body can dispose of. Sodium thiosulfate is then given to increase the capacity for elimination. Methemoglobin can also provide a buffer for a certain amount of cyanide (500 μg/kg of nitroprusside) [7].

Conclusions

SNP an antihypertensive agent is able to generate nitric oxide in the body. The generation of the nitric oxide causes the relaxation of the smooth muscle cells. The reduction of SNP can also generate superoxide in the forming nitric oxide, this generation could go on the produce peroxynitrite. When administering SNP, cyanide is produced which can then be metabolized in the liver and excreted. If a large amount of cyanide is produced, however, cyanide poisoning can

occur. SNP is a powerful vasodilator in treating hypertension and severe cardiac failure it can also be used for the generation of nitric oxide.

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