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Effect of Nitric Oxide Synthase Inhibition on Hemoglobin-Oxygen Affinity and Lipid Peroxidation in Rabbits during Fever

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Key Words

Hemoglobin-oxygen affinity · Lipid peroxidation · Lipopolysaccharide · Fever · Nitric oxide

Abstract

Background: Nitric oxide (NO) is one of the most important biologic messengers and takes part in the development of fever. It can influence on the body prooxidant-antioxidant balance by different ways including interaction with hemoglobin (Hb). ***Methods:*** The effects of nitric oxide synthesis inhibition on the febrile response, hemoglobin-oxygen affinity and parameters of lipid peroxidation were studied in rabbits with fever. The fever was induced by intravenous administration of lipopolysaccharide from *Salmonella typhi* (0.6 μg/kg). Mixed venous blood was taken before the administration and 60, 120 and 180 min after it. The following parameters were measured: half-saturation oxygen pressure (P_{50}), concentrations of conjugated dienes, Schiff bases and α-tocopherol in plasma and red blood cells, and activity of catalase in red blood cells. ***Results:*** The intravenous administration of the nitric oxide synthase inhibitor (N^{ω}-nitro-*L*-arginine; $5 \cdot 10^{-3}$ *M*) reduced the lipopolysaccharide-induced rise in body temperature. After 180 min the actual P_{50} had decreased from 35.0 ± 1.7 to 29.4 ± 1.3 mm Hg. An increase in the lipid peroxidation parameters and a decrease of the antioxidant system indices were observed. The administration of *L*-arginine to prevent nitric oxide synthase inhibition was accompanied by a shift of the oxyhemoglobin dissociation curve rightwards, more marked activation of the free radical processes and a greater elevation of body temperature. The multiple regression analysis showed a close linear correlation between P_{50} and conjugated dienes, Schiff bases, α-tocopherol and catalase. ***Conclusion:*** These results suggest that the increased hemoglobin-oxygen affinity found after the inhibition of nitric oxide synthesis lowers the oxygen flow to tissues and its fraction utilized in free radical oxidations, which finally causes a reduction of the fever response to the lipopolysaccharide.

Introduction

Nitric oxide (NO) is one of the most important biological messengers which mediates endothelium-dependent dilatation of arterial vessels, cytotoxic activity of macrophages, inhibition of platelet aggregation, and serves as a messenger in the nervous system [1]. It is produced from *L*-arginine through catalysis by NO synthase in the presence of reduced nicotinamide adenine dinucleotide phosphate and Ca^{2+} [2]. The activity of NO synthase may be inhibited by *L*-arginine analogs, for example, by its methylated derivatives [3].

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Sometimes the effect of NO synthase inhibition may be favorable for the body, especially during lipid peroxidation (LPO) activation [4]. NO, being a free radical, takes part in the maintenance of the body prooxidant-antioxidant equilibrium [5], both as an oxidant and a radical scavenger. The interaction of NO with superoxide anion is an important mechanism of superoxide inactivation [6]. Hemoglobin (Hb) plays a very important role in the elimination of NO from the body. In arterial blood, NO is inactivated in a reaction with oxyhemoglobin to yield nitrate and methemoglobin, and nitrosohemoglobin is also generated in venous blood [7]; under high PO_2 it may be disintegrated by O_2 to Hb and NO_3^-. The high doses of the NO donor nitroglycerine caused a formation of nitrosohemoglobin in large amounts which correlated with the value of half-saturation oxygen pressure (P_{50}) corresponding to a rightward shift of the oxyhemoglobin dissociation curve (ODC) [8]. Hb exploits conformation-associated changes in the position of $Cys^{\beta 93}$-S-NO to bring the local blood flow into line with oxygen requirements [9]. We had shown that fever led to a change in hemoglobin-oxygen affinity (HOA) with a modulation of LPO activity [10]. The aim of the present work was to study the effect of NO synthesis inhibition on the HOA and free radical lipid oxidation during lipopolysaccharide (LPS)-induced fever in anesthetized rabbits.

Material and Methods

Experimental Protocol

Experiments were carried out in male rabbits (body weight 2.6–3.2 kg) maintained in a vivarium at 20°C and fed ad libitum. A heparinized (100 units/ml) catheter was inserted into the right jugular vein under ether anesthesia for mixed venous blood sampling and injections. Fever was provoked by intravenous administration of *Salmonella typhi* LPS (0.6 μg/kg). The rectal temperature was continuously monitored by an electric thermometer with a sensor which was placed in the rectum at a depth of 5 cm. N^{ω}-Nitro-*L*-arginine (*L*-NNA; Sigma Chemical, St. Louis, Mo., USA) was used for the inhibition of NO synthase. 10^{-3} *M* *L*-NNA (in 4–5 ml of saline) was injected into 13 rabbits. 4 rabbits were supplemented with *L*-arginine (1 m*M* i.v.; Sigma Chemical, St. Louis, Mo., USA) before *L*-NNA. Blood samples were taken before the injection and 60, 120 and 180 min after it.

Blood Preparation

The content of blood gases was measured immediately after the sampling. 3 ml of blood were centrifuged (10 min, 3,000 rpm). The red cell pellet was washed 3 times using 0.9% NaCl and then hemolyzed using bidistilled water (1:5 v/v; 10 min).

Measurement of HOA

PO_2 and acid-base balance were measured with a micro gas analyzer (ABL-330, Radiometer). HOA was assessed by P_{50} (blood PO_2 under its 50% saturation by O_2) as determined by a 'mixing method' [11] at 37°C, pH 7.4 and PCO_2 = 40 mm Hg (P_{50}st). P_{50} at actual pH, PCO_2 and temperature (P_{50}act) were calculated from P_{50}st by Severinghaus' equations [12] and with the temperature coefficient $\Delta \lg P_{50}/\Delta T = 0.024$ [13]; the ODC were calculated by Hill's equation with n = 2.8 from the measured P_{50}.

Lipid Peroxidation

The conjugated diene (CD) content was determined by UV absorption at 232–234 nm (indicating the conjugated double bonds of lipid hydroperoxides) [14]. The results were expressed in relative units of optical density in 1 ml (ΔA_{233}/ml). The level of Schiff bases (SB) was determined by fluorescence intensity of chloroform extracts at excitation and emission wavelengths of 344 and 440 nm, respectively, with an F-4010 spectrofluorimeter (Hitachi). The results were expressed in relative units of intensity in 1 ml of plasma or red blood cells [15].

Antioxidant Defence

Catalase activity was determined by measurement of the rate of decomposition of hydrogen peroxide capable of generating a stable colored complex with molybdenum salts which was measured with an SF-46 spectrophotometer at 410 nm [16]. The α-tocopherol concentration was evaluated by fluorescence intensity of heptane extraction at excitation and emission wavelengths of 292 and 325 nm with an F-4010 spectrofluorimeter (Hitachi) using α-tocopherol (Sigma Chemical Co., St. Louis, Mo., USA) as reference [17]. The protein content was measured according to Layne [18].

Statistics

The data were statistically evaluated by Student's t test with a significance level at $p < 0.05$. The correlations were obtained from the least-squares linear regression analysis. The results are presented as means ± SE. The analyses and graphs were performed using computer software packages (version 3.0, Statgraphics; version 4.0, QUATROPRO).

Results

The LPS administration led to a rise in rectal temperature (fig. 1). It rose in the animals of group 1 (LPS + *L*-NNA) from 38.1 ± 0.18 to 39.0 ± 0.2°C ($p < 0.01$) 120 min after the injection, and in group 2 (LPS + *L*-arginine + *L*-NNA) more markedly from 38.3 ± 0.3 to 40.1 ± 0.2°C ($p < 0.01$) and 39.5 ± 0.2°C ($p < 0.05$) after 120 and 180 min, respectively, without significant differences from the rise in rectal temperature after the injection of LPS alone. The intravenous administration of only *L*-NNA did not significantly change the body temperature.

During fever the values of standard P_{50} were lowered by *L*-NNA from 33.8 ± 1.1 to 28.4 ± 0.98 mm Hg ($p <$

0.01) and 29.74 ± 0.7 mm Hg ($p < 0.01$) after 60 and 180 min, respectively. The actual P_{50} were also decreased by *L*-NNA from 35.0 ± 1.7 to 30.4 ± 0.9 mm Hg ($p < 0.05$) and 29.4 ± 1.3 mm Hg ($p < 0.05$), respectively, indicating a shift of the actual ODC leftwards (fig. 2). The administration of *L*-arginine and *L*-NNA during fever was followed by an increase of P_{50} from 33.7 ± 1.1 to 37.1 ± 1.3 mm Hg after 120 min and a corresponding shift of ODC rightwards. The general pattern of the changes was similar to that observed during LPS-induced fever [10].

Figure 3 shows the changes in LPO activity indices in rabbits of groups 1 and 2. An increase of CD concentrations in plasma and red cells was observed, especially after 120 min of fever [from 1.69 ± 0.25 and 12.09 ± 0.50 to 2.51 ± 0.24 ($p < 0.05$) and 15.89 ± 1.15 ΔA_{233}/ml ($p < 0.01$) in group 1 and from 1.78 ± 0.06 and 11.85 ± 0.43 to 3.05 ± 0.09 ($p < 0.01$) and 21.75 ± 0.48 ΔA_{233}/ml ($p < 0.01$) in group 2]. The plasma and red cell content of SB also rose in group 1 from 6.81 ± 0.72 and 26.33 ± 3.65 to 11.85 ± 1.74 units/ml ($p < 0.01$) and 47.22 ± 6.01 units/ml ($p < 0.01$) after 120 min and to 10.26 ± 0.94 units/ml ($p < 0.01$) and 35.59 ± 1.26 units/ml ($p < 0.05$) after 180 min. In group 2 plasma and red cell SB increased from 6.75 ± 0.48 and 23.75 ± 0.49 units/ml to 17.75 ± 1.11 units/ml ($p < 0.01$) and 94.25 ± 1.44 units/ml ($p < 0.001$) after 120 min and 15.25 ± 0.48 units/ml ($p < 0.01$) and 41.50 ± 0.96 units/ml ($p < 0.01$) after 180 min. Table 1 shows the changes in the main indices of antioxidant activity. The α-tocopherol concentration and catalase activity decreased (most markedly after 120 min of fever). After 120 min, after the inhibition of NO synthesis, plasma and red cell α-tocopherol decreased by 38.9

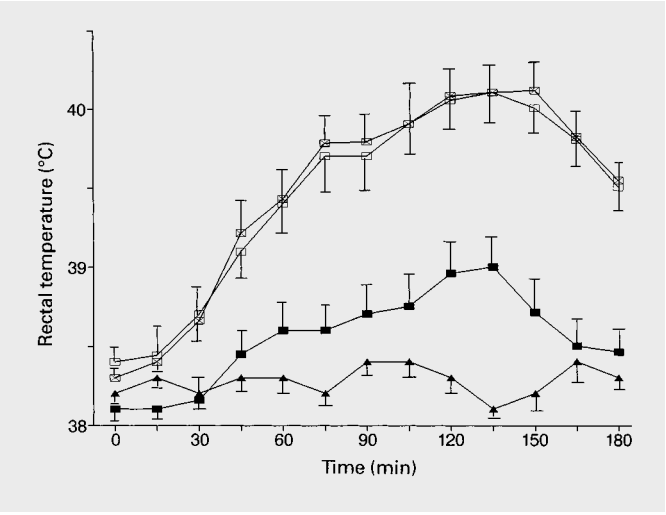

Fig. 1. Changes in rabbit rectal temperature (means ± SE) during the first 180 min after the intravenous administration of LPS + *L*-NNA (■), LPS + *L*-arginine + *L*-NNA (□), LPS (⊠) and *L*-NNA (▲).

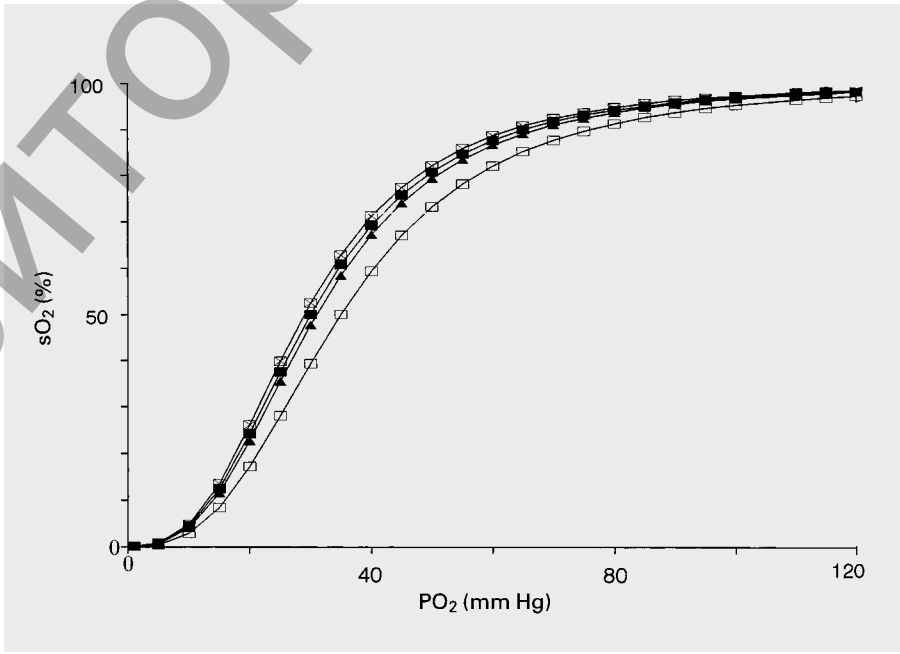

Fig. 2. Actual ODC for mixed venous blood during fever with inactivation of NO synthase: basal (□), 60 min (■), 120 min (▲) and 180 min (⊠) after the administration of *L*-NNA.

Table 1. Indices of antioxidant activity during LPS-induced fever after NO synthase inhibition

Index	Baseline	Time after administration		
		60 min	120 min	180 min
LPS + *L*-NNA[a]				
α-T_{pl}	2.67 ± 0.31	1.86 ± 0.15*	1.63 ± 0.12*	1.53 ± 0.19*
α-T_{rbc}	15.35 ± 2.29	11.40 ± 0.64*	9.42 ± 0.55*	9.61 ± 0.75*
CAT_{rbc}	22.13 ± 2.77	14.48 ± 1.22*	10.88 ± 1.02*	13.39 ± 1.23*
LPS + *L*-arginine + *L*-NNA[b]				
α-T_{pl}	2.48 ± 0.07	1.67 ± 0.14*	1.24 ± 0.05*	1.47 ± 0.06*
α-T_{rbc}	16.98 ± 0.69	10.70 ± 0.74*	8.37 ± 0.96*	10.28 ± 0.49*
CAT_{rbc}	25.56 ± 1.32	14.25 ± 0.75*	9.5 ± 0.96*	12.83 ± 0.64*

Values represent mean ± SE. * $p < 0.05$ vs. before administration. α-T = α-Tocopherol content (m*M*); CAT = catalase activity (10^4 units/mg of protein). Indices rbc and pl are related to red blood cells and plasma, respectively.

[a] Baseline: n = 9, 60 min: n = 9, 120 min: n = 8 and 180 min: n = 7.

[b] n = 4 in all four groups.

and 38.7%, respectively,and by 50.0 and 50.7% in animals in which the inhibition was prevented. Red cell catalase activity in groups 1 and 2 decreased after 120 min by 50.8 and 62.8%, respectively.

These data, which reflect the blood oxygen-binding properties, activities of free radical processes and temperature homeostasis, were statistically treated by the multiple regression analysis, to obtain a matrix of paired correlation coefficients (table 2). The P_{50}act inversely correlated with the CD and SB (r from –0.44 to –0.70, $p < 0.001$). Red cell and plasma α-tocopherol and red cell catalase had a positive and closer correlation with the actual P_{50} (r = 0.81, 0.56 and 0.61, respectively, $p < 0.001$). The data on the correlations of the body temperature with the parameters of blood oxygen transport and free radical oxidation were interesting (the temperature showed a close direct correlation with the P_{50}, CD and SB, and a slightly weaker negative correlation with the antioxidant indices).

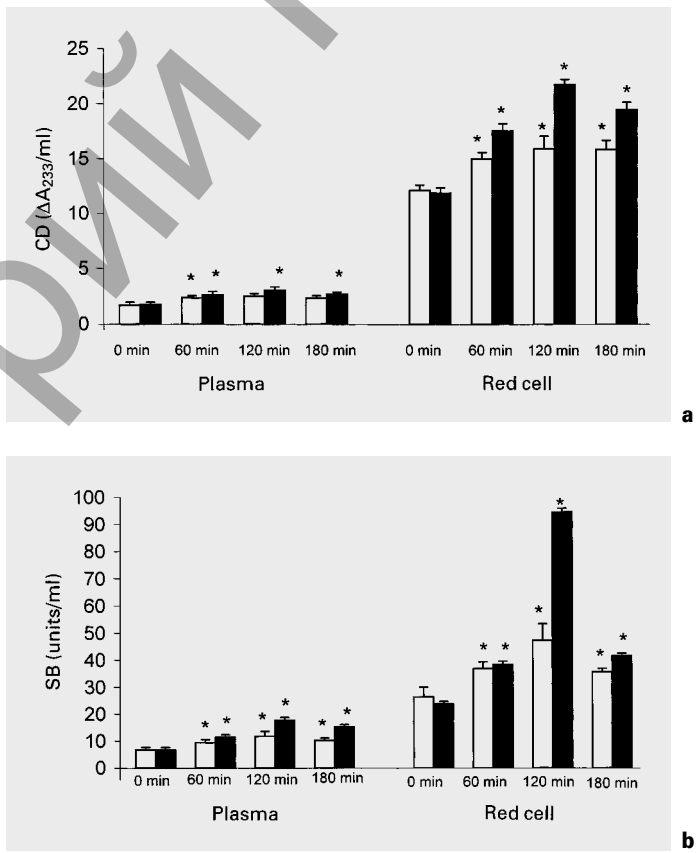

Fig. 3. Changes in contents of CD (**a**) and SB (**b**) in plasma and red cells of mixed venous blood during the first 180 min after administration of LPS + *L*-NNA (□) and LPS + *L*-arginine + *L*-NNA (■) in rabbits. The values are means ± SE. Significant difference from the baseline values is indicated (*).

Discussion

The present work has shown that the inhibition of NO synthase during LPS-induced fever reduced the febrile response and was accompanied by a leftward shift of the ODC and some activation of LPO, whereas the administration of excessive *L*-arginine led to a development of fever and to the shift of the ODC rightwards with a more marked activation of LPO. The analysis of the changes

Table 2. Matrix of paired correlation coefficients between indices of HOA, main indices of LPO and temperature during LPS-induced fever (n = 36)

Indices	P_{50}st	CD_{pl}	CD_{rbc}	SB_{pl}	SB_{rbc}	α-T_{pl}	α-T_{rbc}	CAT_{rbc}	T
P_{50}act	0.77	–0.68	–0.70	–0.44	–0.53	–0.81	0.56	0.61	0.70
P_{50}st		–0.73	–0.80	–0.52	–0.56	0.92	0.55	0.51	–0.73
CD_{pl}			0.68	0.67	0.74	–0.79	–0.78	–0.90	0.72
CD_{rbc}				0.67	0.52	–0.87	–0.41	–0.47	0.93
SB_{pl}					0.83	–0.52	–0.54	–0.63	0.67
SB_{rbc}						–0.57	–0.67	–0.80	0.54
α-T_{pl}							–0.41	–0.45	0.65
α-T_{rbc}								0.82	–0.49
CAT_{rbc}									–0.54

Values are significant coefficients of paired correlation ($p < 0.001$) which reflect moderate or strong relationship between the indices analyzed. P_{50}act = Half-saturation oxygen pressure under actual conditions of temperature, pH and PCO_2; P_{50}st = half-saturation oxygen pressure under standard conditions (37 °C, pH 7.4, PCO_2 40 mm Hg); α-T = α-tocopherol content; CAT = catalase activity. Indices rbc and pl are related to red blood cells and plasma, respectively.

observed in HOA and LPO activity during fever accompanied by NO synthase inhibition makes it possible to distinguish the intrinsic effects of temperature and the influence of LPS. The relatively autonomous intraerythrocyte system of HOA regulation exerts an adaptive change in the blood oxygen-binding properties. The position of the ODC under actual pH, PCO_2 and temperature is a compromise between these differently acting factors.

The rise in body temperature caused by external heat is accompanied by a more marked ODC shift rightwards and LPO activation [19], but under such conditions the NO synthase inhibition results in a more significant increase in free radical oxidation products [20, 21]. The CD and SB concentrations in plasma, red cells and tissues (liver, kidney and heart) significantly rose after the hyperthermia with a preliminary inhibition of NO synthase; during heating the lowering of catalase activity and α-tocopherol content in red cells and tissues was most pronounced in rats receiving this NO synthase inhibitor.

LPS is known to induce a generation of many cytokines (TNF-α, IL-1, IL-6, IFN-α) with a broad range of different effects, including the action on the complement system and the bone marrow stimulation [22]. The latter results in a release of young red cells with higher oxygen affinity [23]. The complement system is very sensitive to LPS and can be activated both in classical (by lipid A via the C1 component) and alternative (by polysaccharide complex via the C3 component) ways [24], having the priming effect and ultimately causing an enhancement of reactive oxygen species production by blood cells. The excessive NO formation is stimulated by cytokines and bacterial LPS and is mediated by an expression of an inducible NO synthase isoform [25]. The inadequate rise of NO, which interacts with superoxide to generate a peroxynitrite, undoubtedly plays an important role in LPO activation [5]. The NO synthase inhibition is also accompanied by a depression of cytokine generation [26], indicating a direct LPS influence on HOA and LPO and its much more complex and multicascade initiating effect on free radical oxidation than that mediated only by temperature.

Many physiological defense mechanisms for temperature homeostasis require energy, but there are also alternative mechanisms diminishing body oxygen demands [27]. The data on the changes in pyrogenic tolerance by NO synthase inhibition and the corresponding changes in HOA and LPO are obviously explained by a depression of nonshivering thermogenesis with a possible involvement of the HOA rise. About 5% of O_2 delivered to tissue mitochondria is converted to reactive oxygen metabolites [14]. These metabolites are usually eliminated by different antioxidant systems. However, under some conditions, such as postischemic reperfusion, their generation may greatly increase and cannot be compensated for by antioxidant defense mechanisms. The value of PO_2 can affect the tissue generation of LPO products.

The problem of LPO oxygen dependence is very important in reperfusion injury, because it was suggested that hyperthermia was accompanied by reoxygenation phenomena [28]. During ischemia a so-called 'oxygen paradox' is observed: the oxidative processes depend on the

O_2 concentration, and when the latter is low, LPO activity is relatively small [29]. During the reperfusion the organ sensitivity to the physiological or higher O_2 content rises, with an activation of LPO. The graded postischemic reoxygenation significantly decreased the levels of LPO products and had a marked neuroprotective effect in rabbits both at early and late periods [30]. The high values of PO_2 in experiments with controlled reoxygenation in immature porcine hearts with cyanosis initiated a burst of oxygen-free radical formation and were associated with a lowering of antioxidant reserve capacity [31]. The increased PO_2 fraction in the gas mixture for isolated ventilated lung during the postischemic period exacerbated tissue injury by a free radical mechanism [32]. The leading role in the LPO initiation obviously belongs to the efficiency of the oxygen utilization mechanisms (determined by the amount of the generated free radicals and the activity of their scavenging) rather than to the absolute oxygen content.

Our previous investigation had shown that the shift of the ODC rightwards during fever closely correlated with the parameters of free radical oxidation [10]. This finding allowed us to consider HOA as one of the physiological mechanisms participating in maintaining the body prooxidant-antioxidant balance. The rise in HOA observed and the corresponding shift of the ODC leftwards limited the oxygen flow to tissues. The processes of lipid-free radical oxidation decrease the coupling of oxidative phosphorylation and tissue respiration. Their activation enhances the processes of energy dissipation, and therefore they may be considered as a mechanism of increasing metabolic heat production. The observed shift of the ODC to the left, with the limitation of the oxygen flux to tissues, may decrease the oxygen fraction utilized in free radical oxidations. This hypothesis was supported by the data of regression analysis, which is confirmed by the close correlation between HOA and the parameters of free radical oxidation during NO synthesis inhibition under conditions of fever.

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