Nitric Oxide 54 (2016) 15–29

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox

Review

Dinitrosyl iron complexes with thiol-containing ligands as a "working form" of endogenous nitric oxide☆

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ARTICLE INFO

Article history:
Received 30 October 2015
Received in revised form
18 January 2016
Accepted 21 January 2016
Available online 26 January 2016

Keywords:
Nitric oxide
Dinitrosyl iron complexes

ABSTRACT

The material presented herein is an overview of the results obtained by our research team during the many years' study of biological activities and occurrence of dinitrosyl iron complexes (DNIC) with thiol-containing ligands in human and animal organisms. With regard to their dose dependence and vast diversity of biological activities, DNIC are similar to the system of endogenous NO, one of the most universal regulators of biological processes. The role of biologically active components in DNIC is played by their iron-dinitrosyl fragments, $[Fe(NO)_2]$, endowed with the ability to generate neutral NO molecules and nitrosonium ions (NO^+). Their release is effected by heme-and thiol-containing proteins, which fulfill the function of biological targets and acceptors of NO and NO^+. Beneficial regulatory effects of DNIC on physiological and metabolic processes are numerous and diverse and include, among other things, lowering of arterial pressure and accelerated healing of skin wounds. In the course of fast decomposition of their $Fe(NO)_2$ fragments (e.g., in the presence of iron chelators), DNIC produce adverse (cytotoxic) effects, which can best be exemplified by their ability to suppress the development of experimental endometriosis in animals. In animal tissues, DNIC with thiol-containing ligands are predominantly represented by the binuclear form, which, contrary to mononuclear DNIC detectable by the 2.03 signal, is EPR-silent.

The ample body of evidence on biological activities and occurrence of DNIC gained so far clearly demonstrates that in human and animal organisms DNIC with thiol-containing ligands represent a "working form" of the system of endogenous NO responsible for its accumulation and stabilization in animal tissues as well as its further transfer to its biological targets.

Contents

Abbreviations: B- or M-DNIC, binuclear or mononuclear dinitrosyl iron complex; DTT, dithiothreitol; EMT, endometrioid tumours; MAP, mean arterial pressure; MNIC-DETC, mononitrosyl iron complexes with diethyldithiocarbamate; MNIC-MGD, mononitrosyl iron complexes with N-methyl-D,L-glucamine dithiocarbamate; RS-NO, S-nitrosothiol.

☆ To the memory of Lyudmila Nikolayevna Kubrina as a token of her inestimable contribution to the study of DNIC in biological systems

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http://dx.doi.org/10.1016/j.niox.2016.01.006
1089-8603/

1. Introduction

It has been established that nitric oxide (NO), one of the simplest chemical compounds synthesized by enzymatic route by virtually all representatives of the world fauna, plays the role of a universal regulator of an immense variety of metabolic processes occurring in living organisms. In human and animal tissues, this compound is formed by oxidation of one of amino groups in the guanidine residue of L-arginine. This reaction is catalyzed by constituitive isozymes of NO synthase (NOS), including endothelial and neuronal NO synthases (eNOS and nNOS, respectively) and inducible (iNOS) NO synthase, and is terminated by the conversion of L-arginine into L-citrulline and a subsequent release of free NO [1–3].

The nature of biological (including beneficial (regulatory) or harmful (cytotoxic)) effects of NO is determined by its steady-state concentration, which does not normally exceed several μM (e-NOS and n-NOS) or ≥ 100 μM (iNOS). These values were cited in review [4] (1996) aimed at a comparison of the calculated concentration of NO consumed in cells and tissues by mitochondria to the amount of NO oxidized by oxygen. The experimental verification of these data by electrochemical methods established that the functioning of iNOS in animal tissues indeed increases the concentration of NO [5–7] In the above-cited studies, it did not exceed 1 μM. Such a low concentration can be attributed to the fact that measurements of NO concentration were performed in the vicinity of the electrode but not in the whole bulk of the tissue [5,7] In the state-of-the art, the determination of NO levels in body tissues by accumulation of NO oxidation products, viz., nitrite and nitrate, or the estimation of NO by its binding to its spin traps, viz., iron complexes with dithiocarbamates, seem to be a more reliable. For example, the use of these spin traps revealed that the mean rate of NO accumulation in mouse liver cells was 7 μmoles of NO per kg of wet tissue (7 μM NO) within 30 min. In animals with inflammation caused by their treatment with bacterial lipopolysaccharide, the concentration of NO was as high as 500 μM NO [8]. This finding illustrates the general pattern defining the beneficial (regulatory) and harmful (cytotoxic) effects of NO, viz., while the former reflect the functional activity of e-NOS and n-NOS, the latter manifest themselves in the appearance of iNOS in body tissues.

There exist quite a few mechanisms responsible for the cytotoxic activity of NO [1,9] circumstance notwithstanding, the majority of investigators adhere to the opinion that NO conversion into peroxynitrite is the most plausible and efficient mechanism underlying the cytotoxic effect of NO [10,11] While peroxynitrite ($ONOO^-$) is formed in the course of NO interaction with the superoxide, its protonated form generates highly reactive hydroxyl free radicals ($OH^•$). At high concentrations of $OH^•$, the latter counteract the antioxidative protective system of the cell and thus exert their cytotoxic effect.

As regards beneficial (regulatory) effects of NO, their realization is possible only under conditions preventing enhancing formation of peroxynitrite from NO as a result of oxidation. This reaction proceeds at a very fast rate because of the free-radical nature of its main participants, viz., NO and the superoxide. However, the efficiency of this process can decrease drastically after incorporation of NO into its endogenous derivatives, viz., S-nitrosothiols (RS-NO) [12–18] and dinitrosyl iron complexes (DNIC) with thiol-containing ligands [19–25]. By virtue of their high stability, NO accumulated in the organism begins to migrate freely both in the cell interior and the intercellular space and, in doing so, effects targeted delivery of NO to biological objects.

Exogenous low-molecular DNIC with thiol-containing ligands easily obtainable by chemical synthesis possess a vast array of biological activities, which mimic those of endogenous NO [19–21]. In-depth studies have shed additional light on the extent to which these complexes are recognized as “working forms” of endogenous NO responsible for its functioning as a universal regulator of major metabolic processes. Our most recent findings and the results of our previous studies strongly suggest that DNIC with thiol-containing ligands represent a unique form of endogenous NO. The present review is an attempt to support this statement by conclusive experimental evidence.

In our previous reviews devoted to the physico-chemistry and biology of DNIC with thiol-containing ligands [19–21,24], the main attention was given to their mononuclear form (M-DNIC) detected in biological objects by the EPR method. The necessity of reconsidering the relevant data stems from our most recent discovery that in animal and bacterial cells DNIC with thiol-containing ligands are predominantly represented by the binuclear (EPR-silent) form.

I would like to begin my communication with a brief survey of the current data on the nature and physico-chemical and biological characteristics of DNIC considered in our previous publications.

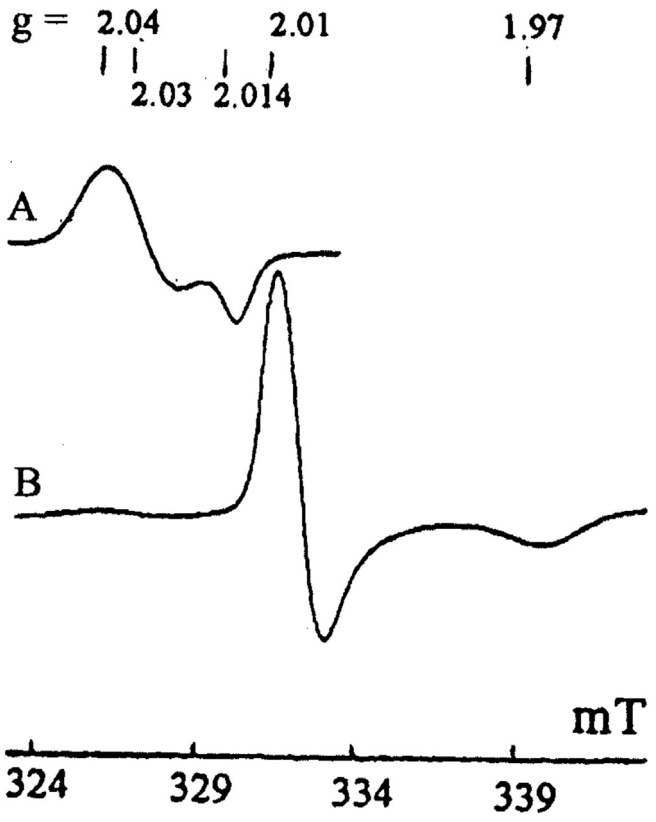

Fig. 1. The EPR spectra of M-DNIC with thiol-containing ligands (A) and the reduced form of M- and B-DNIC with thiol-containing ligands (B) recorded at 77K [38].