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Review

Photochemical delivery of nitric oxide

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ABSTRACT

There remains considerable interest in developing methods for the targeted delivery of nitric oxide and other small molecule bioregulators such as carbon monoxide to physiological targets. One such strategy is to use a "caged" NO that is "uncaged" by excitation with light. Such photochemical methods convey certain key advantages such as the ability to control the timing, location and dosage of delivery, but also have some important disadvantages, such as the relatively poor penetration of the ultraviolet and visible wavelengths often necessary for the uncaging process. Presented here is an overview of ongoing studies in the author's laboratory exploring new photochemical NO precursors including those with nanomaterial antennas designed to enhance the effectiveness of these precursors with longer excitation wavelengths.

Contents

Introduction

The purpose of this article is to provide an overview of studies in my laboratory relevant to the delivery of small molecule bioregulators to physiological targets. Our approach and that of others to more controlled, specific delivery is to develop stable compounds that release the molecule in question only when triggered by an external signal, namely photo-excitation of an appropriate precursor. The precursor is in principle inactive, hence the bioactive agent of interest is "caged", but upon photoexcitation, the latter species is released ("uncaged") (Scheme 1). Although we have focused primarily on the delivery of nitric oxide [1–3], these strategies should apply to other chemotherapeutic molecules such as carbon monoxide, which has also drawn our recent attention [4–6]. For CO, the term "photoCORM" (for photoactivated CO releasing moiety) has been coined [4] to designate a photochemical CO precursor, and, while no such term has caught on with NO precursors, one now hears "photoNORM" used occasionally. The advantage of photo-activation is that the external signal allows one to define the *location* and *timing* of the NO delivery. Furthermore, since the amount of photochemical reaction is a function of the quantity of light delivered to the desired target, this allows one also to define the *dosage* of the release. Although the present manuscript is focused largely upon our own studies, it should be noted that there is a growing interest in applying photochemical methods to the uncaging of NO [7–12] and CO [5,13–14] as well as other bioregulators [15].

Various rationales for controlled NO delivery range include its cardiovascular effects, antibacterial properties and potential roles in generating apoptosis in tumor cells. With regard to cancer therapy, one problem is that, although high localized levels of NO can induce cell apoptosis, low levels of NO may induce tumor growth instead [16]. Thus, it is essential to have very careful control over the dosage delivered. In this context our interest in the photothera-peutic NO delivery draws from the view that this should be synergistic with other forms of treatment. For example, it has been shown that NO increases the sensitivity of tumor cells to radiation therapy [17] and chemotherapy [18]. The hypoxic regions of malignant tumors are much more radio-resistant than is normoxic tissue, therefore one should be able to reduce the collateral damage from radiotherapy by developing strategies to increase the

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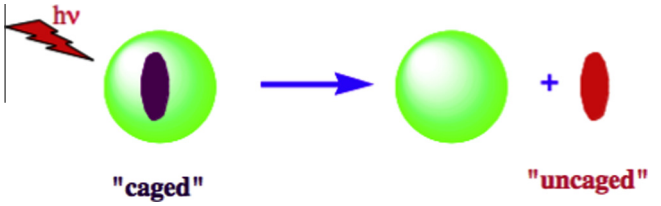


Scheme 1. Cartoon illustrating the photochemical uncaging of a bioactive substance which in the original "caged" form (presumably some type of conjugate) is not active.

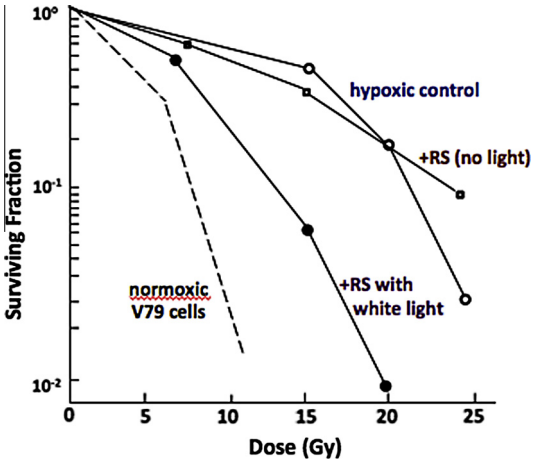


Fig. 1. Survival of V79 Chinese hamster lung cells exposed to γ-radiation under hypoxic conditions without (open circles) or with 500 mM Roussin's red salt (RS) under simultaneous irradiation with white light (closed circles) or in the dark (open squares). The dashed line on the plot indicates the response of V79 cells exposed to γ-radiation under normoxic conditions (WL refers to white light illumination. (Adapted with permission from ref. 20 Copyright 1997 American Chemical Society.).

sensitivity of the targeted tissue. Hypoxia radiation resistance may be alleviated by introducing a sensitzer and/or a vasodilator to increase tissue oxygenation; both are roles played by NO. Radiation sensitization requires NO concentrations near 1 μM [17], but vasodilation is triggered at much lower concentrations of NO [19], so that even at very low concentrations, exogenously delivered NO may indirectly enhance the radiation killing of tumor tissue.

An example of such radiation sensitization is illustrated in Fig. 1. In this case, four different samples of V-79 (Chinese hamster lung fibroblast cells) were subjected to γ-radiation from a Co-60 source in an equivalent manner and the resulting cell viability evaluated [20]. One cell sample was under aerobic conditions, and it is easily seen that less than 1% of the cells were still viable after a γ-radiation dose of ~11 Gy. In contrast, hypoxic cells proved to be much more resistant, with radiation doses exceeding 25 Gy to achieve a comparable effect. The same cells incubated with a 500 μM solution of the photochemical NO donor Roussin's red salt $Na_2[Fe_2S_2(NO)_4]$ (RRS, see below) showed no enhancement of the radiation effect, but when a comparable sample was also illuminated with light from a simple 35 mM projector, a marked enhancement of the radiation damage was apparent. Given that these results paralleled those observed when other NO donors were utilized, it was concluded that the photochemical release of NO from the RRS is responsible for the observed sensitization [20].

With regard to carbon monoxide, it has long been known that CO is produced endogenously by heme oxygenases, and there are newer developments indicating that endogenously and/or exogenously produced CO may be cytoprotective during inflammation, promote wound healing, and have signaling properties for examples: [21,22]. In addition various CO donors have been shown

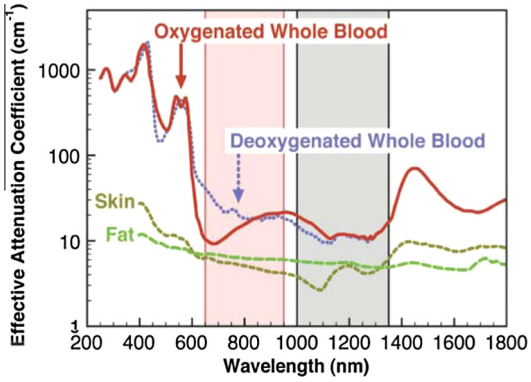
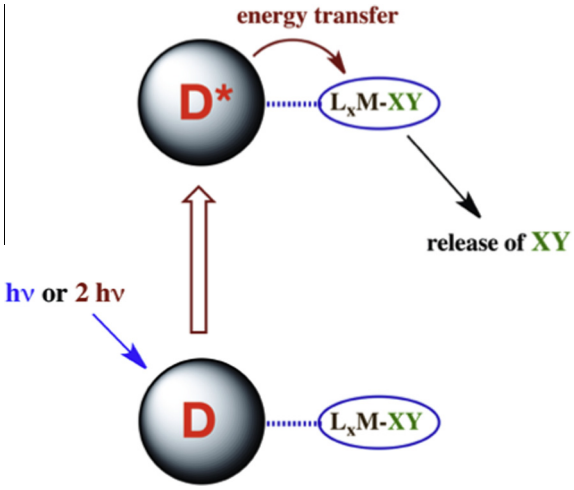


Fig. 2. Absorption properties of various tissue components showing the windows in the near-infrared spectral region (adapted from ref. 26 with permission from the Nature Publishing Group. Original figure provided by Dr. A. Smith of Emory University).



Scheme 2. Single- or two-photon excitation of an antenna/photochemical precursor conjugate leading to release of XY (CO or NO). D is the donor molecule acting as an antenna to absorb light give an excited state D* that undergoes energy transfer to the acceptor molecule L_xM-XY, which is represented here as a metal complex that releases X–Y after the energy transfer step.

in animal studies to be effective in alleviating ischemia/reperfusion (I/R) injury in various organs and tissues for examples: [23–25].

Strategies for and problems with developing methodologies for photochemical CO and NO release show certain parallels. One property desirable for a photochemical precursor would be solubility in aqueous solution or (perhaps) in a medium such as aqueous dimethylsulfoxide (DMSO) that is commonly used for drug delivery. Another would be reasonable stability in aerated aqueous media at physiological temperatures and other conditions typical to living organisms. A third would be photoreactivity at wavelengths where the transmission of light is optimal (Fig. 2) [26].

Penetration depth of light into tissue is strongly wavelength dependent. It is shallow for ultraviolet light, but improves for longer visible wavelengths and tissue penetration reaches its deepest values in the near infrared (NIR) spectral region (~700–1100 nm).

Photochemical activation at these longer wavelengths might be accomplished by using antenna chromophores having high extinction coefficients at the desired wavelengths (Scheme 2). However, such an antenna can be an effective photosensitizer only if there are acceptor states on the precursor molecule having the appropriate energies. A more ambitious approach would be to utilize an antenna with a high two-photon excitation (TPE) cross-section in the NIR. For such a system, excitation with a NIR laser could generate

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