Light and glutathione as selective triggers for the generation of NO and HNO from *trans*-[Fe(cyclam)(NO)Cl]Cl_2

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Nitric oxide (NO) and nitroxyl (HNO) have caught expressive attention of the scientific community due to their roles in several physiological processes, including hypertension, heart failure, cancer, among others.[1] The development of suitable NO donors have evolved well, while HNO donors is only slowly emerging. However, in both cases there is an expressive lack of iron-based candidates. Sodium nitroprusside (SNP) is indeed the only metal complex used clinically with release of NO, but there are problems associated with their use, including photosensitivity and release of cyanide.[2] Therefore, newer iron-based compounds have been sought as alternatives, since large number of ruthenium-based agents have been investigated. Here, we investigated the chemical reactivity and stability of the *trans*-[Fe(cyclam)(NO)Cl](Cl)$_2$ (I). This metallonitrosyl compound showed the actual release of NO under physiological conditions and also upon light stimulation. The half-life time ($t_{1/2}$) for the NO release was 115 min ($k = 0.1x10^{-3}$ s^{-1}) under light irradiation and 385 min ($k = 3.0x10^{-5}s^{-1}$) for thermal release at 37 °C, as measured with cPTIO probe. Myoglobin assay further supported the release of NO under those conditions. However, upon reaction with glutathione, there was strong evidence of the main production of HNO as supported by EPR (Fig. 1A) and myoglobin assay. Additionally, this complex showed direct and fast reaction with superoxide ion suggesting a potential antioxidant action. Vasodilation assay showed promising activity for the *trans*-[Fe(cyclam)(NO)Cl]$^{2+}$ complex (Fig. 1B), along with its low cytotoxicity. Altogether, these studies support a synergistic action of this compound as releasing NO/HNO, which deserves further pharmacological investigations.

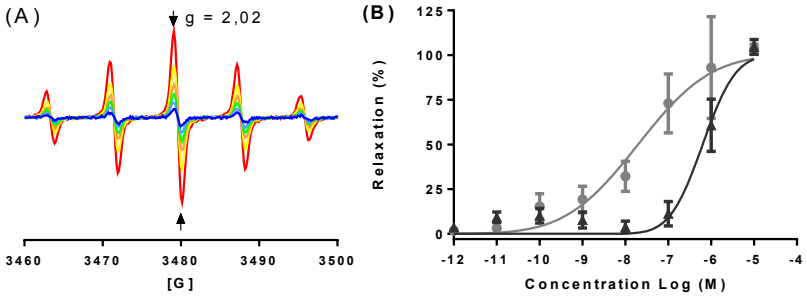

Figure 1. (A) Changes in the EPR spectra during the reaction of I with GSH. (B) Relaxation induced by I (—) and SNP (—) in rat aortic rings pre-contracted with phenylephrine (1,0 μM).

1. Silva, E. H. S.; Ridnour, L. A.; Gouveia, F. S.; Silva, C. D. S.; Wink, D. A.; Lopes, L. G. F.; Sadler, P. J.; *ACS Chem. Biol.,* (DOI: 10.1021/acschembio.6b00222)
2. Roncaroli, F.; Eldik, R.; Olabe, J. A.; *Inorg. Chem.* **2005**, 44**,** 2781.

We thank to CAPES, CNPq (LGFL 303732/2014-8; EHSS 312030/2015-0), FUNCAP/PRONEX (PR2-0101-00030.01.00/15) for financial support.