of an active intracellular or membrane-associated form of gelatinase that is not accessible to TIMP-1 in the culture medium.

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NO comments

SIR — Lipton *et al.*[1] mention two redox-based forms of nitric oxide, one neuroprotective (NO^+, nitrosonium ion) and the other neurotoxic ($NO^•$; neutral nitric oxide with a single electron in an anti-bonding orbital). But there is another redox form of $NO^•$, the nitroxyl anion (NO^-) which Lipton *et al.* do not mention in their *Nature* paper. In an earlier paper[2], however, some of the same authors reported that the nitroxyl anion rapidly converts to nitrous oxide (N_2O) through dimerization and dehydration. They showed the importance of this process for bio logical systems by demonstrating that $NO^•$ converts to NO^- by enzymatic reductase pathways in bacteria.

Bacterial nitric oxide reductases can convert nitric oxide to nitrous oxide as part of the nitrogen cycle[3]. If these nitric oxide reductases have been conserved in mammalian species, then the possible role of nitrous oxide as an endogenous neurotransmitter would have to be evaluated because exogenous nitrous oxide has previously been shown to have a direct influence on neurotransmission at biologically relevant concentrations[4,5]. The conversion of nitric to nitrous oxide would also offer another means of detoxifying nitric oxide, because nitrous oxide is orders of magnitude less toxic than nitric oxide[6].

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SIR — Lipton *et al.*[1] address the observation that sometimes $NO^•$ is toxic, and sometimes it isn't. They argue convincingly that toxicity comes from $NO^•$ reacting with superoxide to form $ONOO^-$, which is a strongly oxidizing agent[7] involved in deleterious processes[8], and that protection results if a compound in which $NO^•$ is present as NO^+ nitrosylates a sulphydryl group of the NMDA receptor, which indirectly prevents $NO^•$ formation. Thus, $NO^•$ is bad, and NO^+ is good. Triplet NO^- should be added to the list and classified as bad, because it reacts rapidly with dioxygen to form $ONOO^-$ (ref. 9).

In his helpful News and Views article[10] on the paper by Lipton *et al.*[1], Snyder suggests that "the designation nitric oxide should be restricted to the reduced, $NO^•$ form of the molecule, while the parent NO should be called 'nitrogen monoxide', and the oxidized form NO^+, the nitrosonium ion." As a member of the IUPAC committee for the nomenclature of inorganic chemistry I would like to caution against these recommendations for two reasons.

First, the difference between '$NO^•$' and 'parent NO' is unclear. Second, there are recommended names for NO^+, $NO^•$ and NO^-, namely nitrosyl cation, nitrogen monoxide and oxonitrate(1^-) anion, respectively[11]. We do not recommend the commonly used name for $NO^•$, nitric oxide, because the suffix '-ic' can suggest an oxidation state that is not always the same. As an example, the oxidation state of nitrogen in nitric oxide is 2+, but it is 5+ in nitric acid.

Nitrogen monoxide is a perfectly systematic name for $NO^•$ when one considers that $NO_2^•$ is named nitrogen dioxide. The name oxonitrate(1^-) for NO^- sounds odd, but it makes sense next to the systematic names dioxonitrate(1^-) for nitrite, and trioxonitrate(1^-) for nitrate. Similarly, the recommended name for peroxynitrite or peroxonitrite is oxoperoxonitrate(1^-). I realize that many working in the rapidly expanding nitric oxide — oops! — nitrogen monoxide field will be reluctant to accept and use these names, but they are easier to learn than the old ones.

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LIPTON *ET AL.* REPLY — The divergence in the views expressed by Gillman and Lichtigfeld and by Koppenol on the 'virtue' of NO^- illustrates an important point: the propensity of various NO congeners for toxic or protective actions is determined by the chemistry that they undergo in specific cellular milieux[2]. We also suggest that the thiol mediated formation of hydroxylamine (NH_2OH) from NO^- could, in many biological systems, be the preferred NO^- reaction pathway, and thus serve to detoxify $NO^•$. NO^+ (or the group transfer there of) is mutagenic when *N*-nitrosation of DNA leads to deamination, but is protective when *S*-nitrosation leads to down-regulation of NMDA receptor activity. $NO^•$ exerts numerous salutary effects through activation of guanylate cyclase, but also manifests peroxynitrite-mediated cytotoxic actions. Designation of the various redox-related forms of NO as 'good' or 'bad' should in our view be avoided.

Koppenol brings the authority of IUPAC, and an appealing whimsy, to bear on the issue of NOmenclature. We use 'NO' as a generic, family name that embraces the specific species NO^-, $NO^•$ and NO^+. This usage, carefully defined in our publications (see ref. 1), is handy in broad discussions of NO-group transfer reactions — particularly in biological systems where the nature of the species transferred (NO^-, $NO^•$, NO^+) is not known with certainty, and the character of the NO moiety in bioactive substances is ambiguous[2]. We deliberately introduced this usage[1] to expand the perspectives on NO action: the integration of the distinctive chemistries of NO^-, $NO^•$ and NO^+ within the field of 'nitric oxide' biology is critical to an understanding of the 'Janus faces' of NO.

We endorse the suggestion of Snyder[10] that biomedical researchers recognize these distinctions and adhere to an unambiguous NOmenclature. We concede that a defect of our scheme is the possible confusion that could arise from the common tendency to write $NO^•$ simply as 'NO' — IUPAC recommendations notwithstanding. With the conviction that people in the field have come to appreciate the significance of the broader chemistry of 'NO', we defer to IUPAC — despite misgivings about $OONO^-$ being termed 'oxoperoxonitrate(1^-)' (personally we prefer 'Oh NO') — and formally offer NO further comment on the issue of NOmenclature.

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