Letter to the Editor

S·Nitrosoalbumin Plasma Levels in Health and Disease: Facts or Artifacts? Value of Analytical Chemistry in Nitric Oxide Clinical Research

To the Editor:

The discovery of the endothelium-derived relaxing factor (EDRF), its identification as nitric oxide (NO), and the recognition of its multiple biological functions, especially in the cardiovascular system, are fascinating scientific achievements of the last two decades, an effort that was awarded the Nobel Prize for Medicine in 1998.

Curiously, no other small molecule like NO challenges so many scientists from so very different disciplines. In the literature, there is no further example for the development and application of so wide a spectrum of analytical approaches and methods in recent years that has yielded highly divergent values, often within a range of three orders of magnitude, and has consequently led to numerous deceptive conclusions.

In 1992, Stamler et al 1 reported for the first time that NO circulates in plasma of healthy humans primarily as S·nitrosoalbumin (SNALB; 7000 nmol/L, n=5). Mainly on the basis of this finding, Stamler’s group 1 suggested that SNALB may be a physiological reservoir of NO, by which NO-related actions such as vasodilation are regulated in humans. This highly interesting finding has initiated much scientific work in this area.

Until today, however, there is no solid confirmation, perhaps with a single exception, 2 of Stamler’s originally reported values for endogenous normal plasma levels of SNALB, not even by Stamler himself, who communicated 1 in 1997 that normal SNALB plasma levels may be much lower, ie 200 to 1000 nmol/L.

In 1999, for the first time, we questioned 4 Stamler’s findings on endogenous normal SNALB plasma levels. By means of a fully validated, accurate, and artifact-free GC-MS method, which involves—as the sole method in this area—use of 15N-labeled SNALB (ie, S15N ALB) as internal standard and affinity-column extraction of SNALB and S15N ALB from plasma, we found that SNALB indeed exists physiologically in plasma of humans (181 nmol/L, n=23, healthy volunteers; 161 nmol/L, n=40, patients with hepatic diseases), but at concentrations severalfold smaller than Stamler’s originally reported 1 and even revised values. 3 We have confirmed these values by using cysteine/Cu2+ instead of HgCl2 (authors’ unpublished results, 2002).

In the meantime, many other groups, eg Marley et al, 5 Cannon et al, 6 Moriel et al, 7 and Rossi et al, 8 have also reported that normal SNALB plasma levels of endogenous normal plasma levels of SNALB, not even by Stamler himself, who communicated 1 in 1997 that normal SNALB plasma levels may be much lower, ie 200 to 1000 nmol/L.

Highly divergent values for endogenous plasma levels of SNALB and many other members of the L-arginine/NO pathway raise numerous questions. The most serious question concerns, in our opinion, the stepmother importance attributed to analytical chemistry by researchers, authors, editors, reviewers, and publishers of scientific journals, as well as by commercial companies providing assay kits. Despite the damning evidence for the need of reliable, unquestionable quantitative analytical approaches in this field of research, choice of analytical quantitative methods is directed to simplicity, rapidity, and commercial availability rather than to reliability. This practice does not actually promote science and must therefore be changed by all participants.

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