Hydrogen sulfide: in the aftermath of argininosuccinate lyase and nitric oxide deficiency

To the Editor: It is with interest that we read the article titled “Argininosuccinate Lyase Deficiency” by Nagamani et al.,¹ a GeneTest Review that dealt with argininosuccinate lyase deficiency (ASLD) and its metabolic and clinical implications. The deranged nitric oxide (NO) milieu is a likely predecessor for several of the systemic manifestations and long-term presentations of this inherited urea cycle disorder. Although this calls for a therapeutic intervention with NO donors in the symptomatic management of endogenous nitric oxide depletion,² there are some potential drawbacks. Classical NO donors have been in the market for more than five decades.³ In addition to known contraindications and adverse profiles, their prolonged use has attendant drug tolerance and clinical inefficacy. The variability of median effective dose for different therapeutic benefits also makes it difficult to customize the dosage regimen when wider systemic effects are intended—even newer NO donors designed with tissue specificity have not surpassed the conventional agents in their pharmacokinetic or dynamic characteristics.³ Obviously, the cellular production of NO through NOS is dependent on the availability of the precursor, L-arginine, which is compromised in ASLD. An impromptu alternative is a non-enzymatic mode of NO generation from endogenous nitrite, which is activated or sustained under specific disease states with reduced (acidic) physiological pH.⁴ Although there is limited utilization of exogenous arginine for the NO pathway in ASL,² it may open up another window of indirect physiological activity by increasing the systemic levels of hydrogen sulfide (H₂S).⁴

Studies of reciprocity between the two signaling systems (NO and H₂S) have shown over 10-fold accentuation of H₂S-mediated effects by NO donors.⁵ Recently, scientific evidence has unfolded a multitude of regulatory roles for H₂S (similar to NO), thereby accounting for a shift in our earlier perspective of this “toxic pollutant.”⁶ Coexistent with NO and sharing functions, H₂S is endogenously generated in tissues that are targets of its physiological actions as a direct vasorelaxant or as a neuromodulator. Reports on the delicate nature of cross-talk also include H₂S-mediated NO production by an Akt-dependent mechanism⁷ and formation of sulfinyl nitrite (an NO donor) as a reaction byproduct with peroxynitrite.⁸ Hence, the endogenous H₂S pathway can be a likely contender for the manifestations of the arginine–NO–cGMP system.⁹

While the efforts to understand the biological relevance of having two parallel systems (NO and H₂S) are under way, a number of H₂S-donating drugs are in various stages of clinical development. In view of its ability to target multiple (NO-independent) mechanistic pathways,^{4,6} H₂S has the potential

to be effective in patients with inherent arginine and/or NO deficiency or accompanying endothelial (eNOS) and neurological (nNOS) impairments. In conclusion, the downstream NO insufficiency in patients suffering from ASLD warrants additional strategies to activate alternative effector systems. Future studies are therefore needed to unravel L-arginine- and/or NO-independent and self-reliant treatment modalities, which will improve overall clinical outcome and prevent the long-term complications of this genetic disorder.

DISCLOSURE

The authors declare no conflict of interest.

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doi:10.1038/gim.2012.48

Response to Srilatha et al.

To the Editor: We thank Drs Srilatha, Meng, and Adaikan for their letter “Hydrogen sulfide: in the aftermath of argininosuccinate lyase and nitric oxide deficiency,”¹ regarding therapeutic strategies aimed at treating the nitric oxide (NO) deficiency in subjects with argininosuccinate lyase deficiency (ASLD). The authors suggest the interesting possibility of providing H₂S donors as a therapeutic modality for ASLD instead of NO donors and discuss the potential drawbacks with NO donor therapy.

We agree that long-term NO supplementation for the treatment of conditions such as hypertension in the general