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Gaso-Transmitters: Expanding the kinetic universe of cell signaling

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Central to the homeostatic life of cells is the need to coordinate responses to external and internal changes. These processes become even more important in the context of the sustained cell-cell interactions that take place in multi-cellular organisms. As amply studied in metazoans, intricate mechanisms allow communication between the cell of production (autocrine), as well as similar and dis-similar cells both locally (paracrine) and over great distances (endocrine). These mechanisms of cell communication have been categorized into families of signal transducers and this knowledge has provided an intellectual framework within which to understand the molecular details of the processes. The classic examples of cell-to-cell communication relate to proteins, especially those secreted into the extracellular space. In general, such proteins interact with specific cell membrane receptors to alter membrane protein/domain organization and/or cytoplasmic/organelle and nuclear events and thus cell response. However, communication by secreted proteins is itself limited through the process of diffusion, which for large macromolecules may not be insignificant (10).

Over the last quarter century plus, demonstration of signaling from outside to inside cells via protein ligands and receptors has paralleled technical advances in cell culture, protein biochemistry and antibody development. In contrast, other less cumbersome, more diffusible moieties such as nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) have been known to engage with proteins for some time. As early as 1891, H_2S was reported to interact with hemoglobin (2) and by 1925 this interaction was confirmed for NO (1). However, the meaning of these interactions in terms of human health was not apparent until much later, although the deadly consequences of exposure to CO were known as early as the start of the century (7). As small and highly mobile molecules, NO, CO, H_2S (4), and other recent possible candidates such as ammonia (NH_3), methane (CH_4) and even hydrogen (H^+) or hydroxyl (OH^-), have been classified as gaso-transmitters. As a group, these agents share properties including being gases under physiologically relevant conditions, crossing cell membranes rapidly, being produced biochemically by proteins (excepting hydroxyl radical), and displaying discrete threshold levels of signaling (6). This shift in perspective from toxic agent or pollutant to active and important signaling molecules has promoted an abundance of research. Translational studies have defined roles for these

agents in human health and disease, and this has resulted in clinical studies and in some instances new therapies. The first biogas to reach the clinic as a therapeutic was NO, as an inhaled agent for new-born respiratory failure (1995, NCT00005776). Applications of NO to human disease was initially via surrogates that intersect the NO signaling cascade such as nitroglycerine (3, 9), nitrite/nitrate (8), blockers of phosphodiesterase activity to increase NO's second messenger guanosine monophosphate (5), and recently the gaso-transmitter NO itself (ClinicalTrials.gov Identifier: NCT01089439, others). Although CO (Identifier: NCT01523548, others) and H_2S (Identifier: NCT02899364, others) have been applied in a limited number of trials including phase 3 trials (for CO only), it remains to be seen if these and other biogases or their surrogates will become drugs.

Gaso-transmitter science is advancing rapidly as a dynamic and evolving area of research. In this issue, *AJP-Cell Physiology* begins a Theme of Reviews on Gaso-Transmitters. In the first of this series, Dr. Csaba Szabo of the University of Texas Medical Branch provides a comprehensive review of H_2S (REF 11, Review article in press). We hope that the series of Reviews will expand awareness in the scientific and medical community of these fascinating molecules and may also stimulate increased cross-disciplinary research. We thank the authors for their kind contributions of expert Reviews for this Theme.

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References

1. **Anson ML and Mirsky AE.** On the combination of nitric oxide with haemoglobin. *The Journal of Physiology* 60: 100-102, 1925.
2. **Bruere MA.** Direct action of hydrogen sulphide, hydrogen selenide, and hydrogen telluride on haemoglobin. *Journal of Anatomy and Physiology* 26: 62-75, 1891.
3. **Carlson MD and Eckman PM.** Review of vasodilators in acute decompensated heart failure: the old and the new. *Journal of Cardiac Failure* 19: 478-493, 2013.
4. **Clanton TL, Hogan MC, and Gladden LB.** Regulation of cellular gas exchange, oxygen sensing, and metabolic control. *Comprehensive Physiology* 3: 1135-1190, 2013.
5. **Ghofrani HA, Osterloh IH, and Grimminger F.** Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. *Nature Reviews Drug Discovery* 5: 689-702, 2006.
6. **Mustafa AK, Gadalla MM, and Snyder SH.** Signaling by gasotransmitters. *Science Signaling* 2: re2, 2009.
7. **Nasmith GG and Graham DA.** The haematology of carbon-monoxide poisoning. *The Journal of Physiology* 35: 32-52, 1906.
8. **Omar SA, Webb AJ, Lundberg JO, and Weitzberg E.** Therapeutic effects of inorganic nitrate and nitrite in cardiovascular and metabolic diseases. *Journal of Internal Medicine* 279: 315-336, 2016.
9. **Wei J, Wu T, Yang Q, Chen M, Ni J, and Huang D.** Nitrates for stable angina: a systematic review and meta-analysis of randomized clinical trials. *International Journal of Cardiology* 146: 4-12, 2011.
10. **Zhou HX and Bates PA.** Modeling protein association mechanisms and kinetics. *Current Opinion in Structural Biology* 23: 887-893, 2013.
11. **Szabo C.** ……*Am J Physio - Cell Physio* Vol: pages, 2016.