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Gasotransmitters: Expanding the kinetic universe of cell signaling

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

52 Over the last quarter century plus, demonstration of signaling from outside to inside cells via
53 protein ligands and receptors has paralleled technical advances in cell culture, protein biochemistry and
54 antibody development. In contrast, other less cumbersome, more diffusible moieties such as nitric oxide
55 (NO), carbon monoxide (CO) and hydrogen sulfide (H₂S) have been known to engage with proteins for
56 some time. As early as 1891, H₂S was reported to interact with hemoglobin (2) and by 1925 this
57 interaction was confirmed for NO (1). However, the meaning of these interactions in terms of human
58 health was not apparent until much later, although the deadly consequences of exposure to CO were
59 known as early as the start of the century (7). As small and highly mobile molecules, NO, CO, H₂S (4),
60 and other recent possible candidates such as ammonia (NH₃), methane (CH₄) and even hydrogen (H⁺) or
61 hydroxyl (OH⁻), have been classified as gaso-transmitters. As a group, these agents share properties
62 including being gases under physiologically relevant conditions, crossing cell membranes rapidly, being
63 produced biochemically by proteins (excepting hydroxyl radical), and displaying discrete threshold levels
64 of signaling (6). This shift in perspective from toxic agent or pollutant to active and important signaling
65 molecules has promoted an abundance of research. Translational studies have defined roles for these

66 agents in human health and disease, and this has resulted in clinical studies and in some instances new
67 therapies. The first biogas to reach the clinic as a therapeutic was NO, as an inhaled agent for new-born
68 respiratory failure (1995, NCT00005776). Applications of NO to human disease was initially via
69 surrogates that intersect the NO signaling cascade such as nitroglycerine (3, 9), nitrite/nitrate (8), blockers
70 of phosphodiesterase activity to increase NO's second messenger guanosine monophosphate (5), and
71 recently the gaso-transmitter NO itself (ClinicalTrials.gov Identifier: NCT01089439, others). Although
72 CO (Identifier: NCT01523548, others) and H₂S (Identifier: NCT02899364, others) have been applied in a
73 limited number of trials including phase 3 trials (for CO only), it remains to be seen if these and other
74 biogases or their surrogates will become drugs.

75 Gaso-transmitter science is advancing rapidly as a dynamic and evolving area of research. In this
76 issue, *AJP-Cell Physiology* begins a Theme of Reviews on Gaso-Transmitters. In the first of this series,
77 Dr. Csaba Szabo of the University of Texas Medical Branch provides a comprehensive review of H₂S
78 (REF 11, Review article in press). We hope that the series of Reviews will expand awareness in the
79 scientific and medical community of these fascinating molecules and may also stimulate increased cross-
80 disciplinary research. We thank the authors for their kind contributions of expert Reviews for this Theme.

81

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86

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