

Themed Section: Pharmacology of the Gasotransmitters

EDITORIAL Pharmacology of the 'gasotransmitters' NO, CO and H₂S: translational opportunities

DOI:10.1111/bph.13005 www.brjpharmacol.org

Correspondence

Péter Ferdinandy, Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary. E-mail: peter.ferdinandy@ pharmahungary.com

Andreas Papapetropoulos^{1,2}, Roberta Foresti^{3,4} and Péter Ferdinandy^{5,6}

¹*Faculty of Pharmacy, University of Athens, Athens, Greece, ²'George P. Livanos and Marianthi Simou Laboratories', Evangelismos Hospital, 1st Department of Critical Care and Pulmonary Services, University of Athens, Greece, ³Université Paris-Est, UMR_S955, UPEC, F-94000, Créteil, France, ⁴Inserm U955, Equipe 12, F-94000, Créteil, France, ⁵Pharmahungary Group, Szeged, Hungary and ⁶Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary*

LINKED ARTICLES

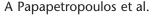
This article is part of a themed section on Pharmacology of the Gasotransmitters. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2015.172.issue-6

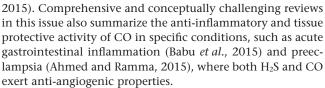
The current themed issue collates a number of reviews and original papers on the pharmacology of NO, CO and H₂S. These three molecules have been grouped together to form a family of signaling mediators that has become known as 'gasotransmitters'. Authors of the articles in this issue are members of ENOG- the European Network On Gasotransmitters (COST Action BM1005, www.gasotransmitters.eu). ENOG currently numbers more than 200 researchers from 24 European Countries and is funded through the European Science Foundation. Work from ENOG researchers and colleagues around the world have contributed to the understanding of the role of these molecules in physiology and disease initiation and progression. In addition, substantial progress has been made in recent years in the pharmacology of CO and H₂S with the development of several CO- and H₂S-donors.

The NO field is more than 3 decades old, but readers can find in this issue reviews on novel aspects of NO/cGMP signaling and on the therapeutic usefulness of components of this pathway in cardiovascular diseases (Papapetropoulos *et al.*, 2015) with or without co-morbidities, such as metabolic diseases (Pechánová *et al.*, 2015). Sexual dysfunction (Yetik-Anacak *et al.*, 2015) and male infertility (Buzadzic *et al.*, 2015) are additional fields where modulation of NO signaling bears therapeutic potential. S-nitrosation, a NO-induced posttranslation modification of proteins is discussed by Santos *et al.* (2015) in the context of neuronal plasticity.

The H₂S field has recently experienced a booming interest as evidenced by the exponentially increasing number of published articles in the field. Papers on the role of H₂S in ischaemic diseases (Bos *et al.*, 2015), as well as blood pressure regulation and hypertension (Snijder *et al.*, 2015; Brancaleone *et al.*, 2015) can be found in this issue. Interactions of H₂S with myeloperoxidase are reported in an original paper by Pálinkás *et al.* (2015); the inhibitory effect of H₂S on myeloperoxidase is expected to contribute to the actions of H₂S in the context of inflammation.

CO is a unique gasotransmitter, as its specific molecular targets are still not known and it is a more stable molecule as compared to NO or H₂S. However, the strong affinity of CO for metal centers can guide us in the search for the putative cellular targets. E.g. mitochondria rich in haeme-iron proteins are potential candidates for molecular targets for CO. This concept is discussed in the review of Queiroga *et al.* (2015) in the context of the role of endogenous and exogenous CO in pathologies of the central nervous system. In addition, ion channels have been recognized as possible effectors of CO signaling and it appears that modulation of the activity of channel proteins is part of the mechanism contributing to the physiological and therapeutic actions of CO (Peers *et al.*,





The interaction of NO, H_2S , and CO at the cellular level can be observed in several pathologies, such as ischaemic heart disease and hypertension, allowing several pharmacological approaches for modulation of these gasotransmitters in order to protect the ischaemic heart with or without co-morbidities (Andreadou *et al.*, 2015) and to regulate blood pressure (Wesseling *et al.*, 2015). Cardiovascular co-morbidities may alter cardioprotective signaling including gasotransmitters, therefore, co-morbidities have to be taken into account when developing cardioprotective therapies as reviewed recently elsewhere (Ferdinandy *et al.*, 2014).

The current issue also contains practical guides for scientists just entering into the interesting field of gasotransmitter research, including technical guidelines to measure NO in biological samples (Csonka *et al.*, 2015), basic guidelines for H₂S pharmacology (Papapetropoulos *et al.*, 2015), and the chemical characteristics and biological behaviors of CO-releasing molecules (Schatzschneider, 2015).

The editors of this themed issue hope that the papers gathered here will be useful for established researchers already involved in gasotransmitter research, as well as for young scientists just planning to enter the field, and for teachers and students interested in the physiology, pathology, and pharmacology of NO, H_2S and CO.

Acknowledgements

Authors acknowledge the support of the COST Action BM 1005. PF is a Szentágothai Fellow of the Hungarian National Program of Excellence (TAMOP 4.2.4.A/2-11-1-2012-0001).

References

Ahmed A, Ramma W (2015). Unraveling the theories of preeclampsia: Are the protective pathways the new paradigm? Br J Pharmacol 172: 1574–1586.

Andreadou I, Iliodromitis EK, Rassaf T, Schulz R, Papapetropoulos A, Ferdinandy P (2015). The role of gasotransmitters NO, H₂S and CO in myocardial ischaemia/reperfusion injury and cardioprotection by preconditioning, postconditioning and remote conditioning. Br J Pharmacol 172: 1587–1606.

Babu D, Motterlini R, Lefebvre RA (2015). CO and CO-releasing molecules (CO-RMs) in acute gastrointestinal inflammation. Br J Pharmacol 172: 1557–1573.

Bos EM, van Goor H, Joles JA, Whiteman M, Leuvenink HGD (2015). Hydrogen sulfide: physiological properties and therapeutic potential in ischaemia. Br J Pharmacol 172: 1479–1493.

Brancaleone V, Vellecco V, Matassa DS,

d'Emmanuele di Villa Bianca R, Sorrentino R, Ianaro A *et al.* (2015). Crucial role of androgen receptor in vascular H₂S biosynthesis induced by testosterone. Br J Pharmacol 172: 1505–1515.

Buzadzic B, Vucetic M, Jankovic A, Stancic A, Korac A, Korac B *et al.* (2015). New insights into male (in)fertility: the importance of NO. Br J Pharmacol 172: 1455–1467

Csonka C, Páli T, Bencsik P, Görbe A, Ferdinandy P, Csont T. (2015). Measurement of NO in biological samples. Br J Pharmacol 172: 1620–1632

Ferdinandy P, Hausenloy DJ, Heusch G, Baxter GF, Schulz R. (2014). Interaction of Risk Factors, Comorbidities, and Comedications with Ischemia/Reperfusion Injury and Cardioprotection by Preconditioning, Postconditioning, and Remote Conditioning. Pharmacol Rev 66: 1142–1174.

Pálinkás Z, Furtmüller PG, Nagy A, Jakopitsch C, Pirker KF, Magierowski M *et al.* (2015). Interactions of hydrogen sulfide with myeloperoxidase. Br J Pharmacol 172: 1516–1532.

Papapetropoulos A, Hobbs AJ, Topouzis S (2015). Extending the translational potential of targeting NO/cGMP-regulated pathways in the CVS. Br J Pharmacol 172: 1397–1414.

Papapetropoulos A, Whiteman M, Cirino G (2015). Pharmacological tools for hydrogen sulphide research: a brief, introductory guide for beginners. Br J Pharmacol 172: 1633–1637.

Pechánová O, Varga ZV, Cebová M, Giricz Z, Pacher P, Ferdinandy P (2015). Cardiac NO signalling in the metabolic syndrome. Br J Pharmacol 172: 1415–1433.

Peers C, Boyle JP, Scragg JL, Dallas ML, Al-Owais MM, Hettiarachichi NT *et al.* (2015). Diverse mechanisms underlying the regulation of ion channels by carbon monoxide. Br J Pharmacol 172: 1546–1556.

Queiroga CS, Vercelli A, Vieira HL (2015). Carbon monoxide and the CNS: challenges and achievements. Br J Pharmacol 172: 1533–1545.

Santos AI, Martínez-Ruiz A, Araújo IM (2015). S-nitrosation and neuronal plasticity. Br J Pharmacol 172: 1468–1478.

Schatzschneider U (2015). Novel lead structures and activation mechanisms for CO-releasing molecules (CORMs). Br J Pharmacol 172: 1638–1650.

Snijder PM, Frenay AS, de Boer RA, Pasch A, Hillebrands J, Leuvenink HGD *et al.* (2015). Exogenous administration of thiosulfate, a donor of hydrogen sulfide, attenuates angiotensin II-induced hypertensive heart disease in rats. Br J Pharmacol 172: 1494–1504.

Wesseling S, Fledderus JO, Verhaar MC, Joles JA (2015). Beneficial effects of diminished production of hydrogen sulfide or carbon monoxide on hypertension and renal injury induced by NO withdrawal. Br J Pharmacol 172: 1607–1619.

Yetik-Anacak G, Sorrentino R, Linder AE, Murat N (2015). Gas what: NO is not the only answer to sexual function. Br J Pharmacol 172: 1434–1454.