

# Contents

<b>Chapter 1 Overview of Gasotransmitters and the Related Signaling Network</b>	<b>1</b>
<i>Rui Wang</i>	
1.1 Conceptualization and Evaluation Systems for Gasotransmitters	2
1.2 Gasotransmitters – Why Does the Terminology Matter?	10
1.3 The Gasotransmitter Signaling Network in Eukaryotes	11
1.3.1 Interaction of Gasotransmitters with Their Producers	12
1.3.2 Interaction of Gasotransmitters with Their Users/Targets	14
1.3.3 Interaction of Gasotransmitters with Their Sensors	19
1.3.4 Interactions Between Gasotransmitters	23
Acknowledgements	24
References	24
<b>Chapter 2 Production of NO – The L-arginine/NOS/NO System</b>	<b>29</b>
<i>B. D. Paul and S. H. Snyder</i>	
2.1 Introduction	29
2.2 Biosynthesis and Sources of NO	30
2.2.1 Biosynthesis of NO from L-arginine	31
2.2.2 Synthesis of NO from Inorganic Nitrates	31
2.2.3 Biosynthesis of NO from Homoarginine	34

---

Metallobiology Series No. 12

Gasotransmitters

Edited by Rui Wang

© The Royal Society of Chemistry 2018

Published by the Royal Society of Chemistry, [www.rsc.org](http://www.rsc.org)

2.3	Regulation of NO Production	34
2.3.1	Spatial Compartmentalization and Localization	34
2.3.2	Modulation at the Level of Enzymatic Activity	35
2.3.3	Metabolic Control of NO Production	35
2.3.4	Regulation by Arginases	36
2.3.5	Regulation by Arginine Transport	36
2.4	Dysregulation of NO Disposition and Disease	37
2.4.1	Nitric Oxide and Cardiovascular Disease	37
2.4.2	Nitric Oxide and the Reproductive System	37
2.4.3	Nitric Oxide and Neurodegeneration	37
2.5	Concluding Remarks	39
	Acknowledgements	39
	References	39
<b>Chapter 3</b>	<b>Production of H<sub>2</sub>S – The L-cysteine/CSE-CBS-MST/H<sub>2</sub>S System</b>	<b>44</b>
	<i>Yi Zhun Zhu</i>	
3.1	Introduction to H <sub>2</sub> S in Mammalian Cells	44
3.2	Production of H <sub>2</sub> S in Mammalian Cells Involving CSE	46
3.3	Production of H <sub>2</sub> S in Mammalian Cells Involving CBS	47
3.4	Production of H <sub>2</sub> S in Mammalian Cells Involving MST	48
3.4.1	Discovery of H <sub>2</sub> S Production by MST	48
3.4.2	Mechanisms for H <sub>2</sub> S Production by MST	49
3.4.3	Tissue Distribution of MST	50
3.4.4	Regulation of H <sub>2</sub> S Production by MST	51
3.5	Relationship between the Production of H <sub>2</sub> S and Polysulfide	51
3.6	Non-enzymatic H <sub>2</sub> S Production in Mammalian Cells	52
3.6.1	Release of H <sub>2</sub> S from Bound Sulfur	52
3.6.2	H <sub>2</sub> S Production from Organic Polysulfides by Thiol Reactions	52
3.6.3	H <sub>2</sub> S Production by Human Erythrocytes	52
3.7	Exogenous H <sub>2</sub> S Donors in Mammalian Cells	52
3.7.1	Naturally Occurring Donors of H <sub>2</sub> S	52
3.7.2	Synthetic H <sub>2</sub> S Donors	53
	References	55

<b>Chapter 4</b>	<b>HO-1-derived CO Is a Regulator of Vascular Function and Metabolic Syndrome</b>	<b>59</b>
	<i>J. Schragenheim, O. Maayan and N. G. Abraham</i>	
4.1	Introduction	59
4.2	Formation of CO	60
4.3	Role of Excessive Heme in Obesity: HO-1-derived CO	61
4.4	Actions of CO on the Vasculature	64
4.5	CO and the Regulation of Blood Pressure	65
4.6	Metabolic Syndrome and Heme Metabolism	67
4.7	Mitochondrial Dysfunction in Metabolic Syndrome	71
4.8	Regulatory Role of HO-1 in Mitochondrial Function and Oxidative Phosphorylation	73
4.9	Oxidative Stress and Mitochondrial Dysfunction	76
4.10	HO-1 Gene Targeting in Obesity and Hypertension	78
4.11	Bioactive Role of Biliverdin/Bilirubin	80
4.12	Bioactive Role of Iron and Ferritin	81
4.13	Therapeutic Potential of the EET-Heme-HO-1-derived CO/Bilirubin	81
4.14	Concluding Remarks	84
	Acknowledgements	84
	References	84
<b>Chapter 5</b>	<b>Production and Signaling Functions of Ammonia in Mammalian Cells</b>	<b>101</b>
	<i>Ziqiang Meng and Rui Wang</i>	
5.1	Introduction	101
5.2	Production and Metabolism of Ammonia	102
5.2.1	Production of Ammonia	103
5.2.2	Transport of Ammonia	107
5.2.3	Removal and Conversion of Ammonia	108
5.3	Physiological Roles of Ammonia as a Gasotransmitter	110
5.3.1	Roles of Ammonia in the Nervous System	110
5.3.2	Effects of Ammonia on the Cardiovascular System	122
5.3.3	Effects of Ammonia on the Immune System	129
5.3.4	Effects of Ammonia on Other Systems	130
5.4	Pathophysiological Roles of Ammonia	132
5.4.1	Cytotoxic Effects and Cell Swelling and Death	132
5.4.2	Energy Metabolism	134

5.4.3	Oxidative/Nitrosative Stress	135
5.4.4	Mitochondrial Permeability Transition	135
5.4.5	Impairments in Learning and Memory	136
5.4.6	Alterations in Gene Expression	136
5.4.7	Toxic Effects of Ammonia on Other Organs	137
5.5	Perspectives	137
	Acknowledgements	139
	References	139
<b>Chapter 6</b>	<b>The Interaction of NO and H<sub>2</sub>S Signaling Systems in Biology and Medicine</b>	<b>145</b>
	<i>Xu Cao and Jin-Song Bian</i>	
6.1	Introduction	145
6.2	Biosynthesis and Metabolism of H <sub>2</sub> S and NO	146
6.2.1	Biosynthesis and Metabolism of H <sub>2</sub> S	146
6.2.2	Biosynthesis and Metabolism of NO	147
6.3	Biochemistry of H <sub>2</sub> S and NO Interactions	147
6.3.1	Mutual Regulation of the Bioavailability of H <sub>2</sub> S and NO	147
6.3.2	The Direct Reaction of H <sub>2</sub> S and NO Generates Bioactive Molecules	149
6.4	Interactions of H <sub>2</sub> S and NO in the Cardiovascular System	149
6.4.1	H <sub>2</sub> S/NO Interactions in the Regulation of Heart Contractility	149
6.4.2	H <sub>2</sub> S/NO Interactions in Cardioprotection	150
6.4.3	H <sub>2</sub> S/NO Interactions in the Maintenance of Vascular Tone	151
6.5	Interaction of H <sub>2</sub> S and NO in Cancer	151
6.6	Interactions of H <sub>2</sub> S and NO in Inflammation	152
6.7	NOSH Compounds Display Therapeutic Benefits	153
6.8	Concluding Remarks	153
	References	155
<b>Chapter 7</b>	<b>Signaling by CO: Molecular and Cellular Functions</b>	<b>161</b>
	<i>Roberta Foresti, Laura Braud and Roberto Motterlini</i>	
7.1	Introduction	161
7.2	Cellular Targets of CO	163
7.2.1	Cytochrome c and Cytochrome c Oxidase	164
7.2.2	Guanylate Cyclase	165

7.2.3	Ion Channels	166
7.2.4	NADPH Oxidase	166
7.2.5	Cystathionine Beta Synthase	167
7.2.6	Heme-dependent Transcription Factors	167
7.2.7	Other Metal-containing Proteins Targeted by CO	168
7.3	CO in the Regulation of Vascular Tone	168
7.4	CO in Cell Proliferation and Apoptosis	170
7.5	CO as a Neurotransmitter	171
7.6	CO in Redox Regulation	173
7.7	CO in Inflammation	175
7.7.1	Anti-inflammatory Activity of the HO-1/CO Pathway	175
7.7.2	Mechanisms Underlying the Anti-inflammatory Activity of CO	178
7.8	CO in the Regulation of Energetic Metabolism	180
7.9	Conclusions	182
	Acknowledgements	183
	References	183
<b>Chapter 8</b>	<b>Production and Signaling of Methane</b>	<b>192</b>
	<i>M. Boros and F. Keppler</i>	
8.1	Introduction	192
8.2	Physico-chemical Properties and Toxicity of CH <sub>4</sub>	193
8.3	Methanogenesis – Biotic and Abiotic Sources in the Environment	193
8.3.1	Abiotic Sources of CH <sub>4</sub> (Including Thermogenic Degradation of Organic Matter)	194
8.3.2	Microbial Methanogenesis – Formation of CH <sub>4</sub> by Archaea	194
8.3.3	Non-archaeal CH <sub>4</sub> Formation in Eukaryotes	195
8.4	Potential Pathways of CH <sub>4</sub> Formation in Eukaryotes	196
8.5	Human CH <sub>4</sub> Production – Archaeal and Non-archaeal Sources	199
8.6	Intestinal Gases and the Influence of CH <sub>4</sub> on Gastrointestinal Motility	202
8.7	Effects of CH <sub>4</sub> on the Metabolism	205
8.8	Interaction with Other Biological Gases: CO, NO, and H <sub>2</sub> S	207
8.9	Bioactivity of Exogenous CH <sub>4</sub>	210

8.9.1	CH <sub>4</sub> Effects in Sterile and Infectious Inflammation	212
8.9.2	Endotoxemia	212
8.9.3	Autoimmune Inflammation	213
8.9.4	Experimental Colitis	213
8.9.5	Ischemia–Reperfusion	213
8.9.6	Neuroprotection	217
8.9.7	Mitochondrial Effects	220
8.10	Mechanism of Action	223
8.10.1	Theory of a Membrane-associated Mechanism of Action	223
8.10.2	CH <sub>4</sub> Accumulation May Indirectly Influence the Intracellular Signaling Reactions that Lead to Anti-inflammatory Effects	225
8.11	Conclusions	226
	Acknowledgements	228
	References	228
<b>Chapter 9</b>	<b>Gasotransmitters in Plants</b>	<b>235</b>
	<i>Yanxi Pei, Zhuping Jin, Zhiqiang Liu, Huihui Fang, Liping Zhang, Xuefeng Hao, Danmei Liu, Xinzhe Du, Yanjie Zhang, Baohua Tian and Xiaoli Ma</i>	
9.1	Nitric Oxide in Plants	235
9.1.1	Introduction to NO in Plants	235
9.1.2	Production of Endogenous NO in Plants	236
9.1.3	Signal Function of NO in Plants	238
9.1.4	Functional Mechanism of NO in Plants	242
9.1.5	Conclusions and Perspectives	247
9.2	Carbon Monoxide in Plants	248
9.2.1	Introduction to CO in Plants	248
9.2.2	Production of Endogenous CO in Plants	248
9.2.3	Physiological Functions of CO in Plants	248
9.2.4	Future of CO in Plants	250
9.3	Hydrogen Sulfide in Plants	250
9.3.1	Introduction to H <sub>2</sub> S	250
9.3.2	Generation of Endogenous H <sub>2</sub> S in Plants	251
9.3.3	Physiological Functions of H <sub>2</sub> S Signals in Plants	252
9.3.4	Function Mechanism of H <sub>2</sub> S in Plants	253
9.4	Ammonia in Plants	257

<i>Contents</i>	xiii
9.4.1 Introduction to NH <sub>3</sub> in Plants	257
9.4.2 Production of Endogenous NH <sub>3</sub> in Plants	258
9.4.3 Signal Function and Mechanism of NH <sub>3</sub> in Plants	259
9.5 Methane in Methanogens and Plants	259
9.5.1 Introduction to CH <sub>4</sub>	259
9.5.2 Production of Endogenous CH <sub>4</sub> in Methanogenic Archaea and Plants	260
9.5.3 Signal Functions and Mechanisms of CH <sub>4</sub> in Plants	264
9.6 Ethylene in Plants	264
9.6.1 Introduction to Ethylene in Plants	264
9.6.2 Production of Endogenous Ethylene in Plants	264
9.6.3 Signal Functions and Mechanisms of Ethylene in Plants	265
9.7 Further Research Prospects	267
Abbreviations	268
References	271
<b>Appendix Gasotransmitters: Growing Pains and Joys</b>	<b>283</b>
<i>Rui Wang</i>	
A.1 Appraisal of the Known Gasotransmitters	284
A.2 Advocacy of Gasotransmitters as Favored Signaling Molecules for Eukaryotes	286
A.2.1 Simplicity	286
A.2.2 Availability	286
A.2.3 Volatility	286
A.2.4 Effectiveness	286
A.3 Ambiguity of the Interactions among Gasotransmitters and the Significance of Their Crosstalk	287
A.4 Additions to the Gasotransmitter Family	287
A.4.1 Ammonia (NH <sub>3</sub> )	288
A.4.2 Methane (CH <sub>4</sub> )	290
A.4.3 Hydrogen Gas (H <sub>2</sub> )	292
A.5 Concluding Remarks	292
Acknowledgements	293
References	293
<b>Subject Index</b>	<b>296</b>

