Preface

From ancient Greek philosophers the idea evolved that an "animalic spirit" called "pneuma" pervades through our body acting primarily at the brain, the heart, and the liver. As a vital force it allowed the various parts of the body to communicate with each other. This idea survived several 100 years—longer than most of our present hypothesis.

It came as a great surprise to the scientific community when researchers discovered that poisonous gases, endogenously produced by a great variety of living organisms from bacteria to men, exert important intra- and intercellular tasks—kind of reviving the pneuma idea. Since the epochal discovery of the radical nitric oxide (NO) as gaseous signaling molecule two other gases—carbon monoxide (CO) and hydrogen sulfide (H_2S)—have been found to be also involved in a plethora of physiological and pathophysiological functions. The gases, now a family of at least three, have been termed "gasotransmitters". A definition of molecules to be classified as gasotransmitters is given by Untereiner et al. in their chapter. The most prominent features that characterize the gases and discriminate them from classical transmitters are their amphiphilic chemical nature that allows them to diffuse in the cytosol as well as through lipid membranes which prevents them from being stored in vesicles. The gases, because of their small size and hence high diffusion rate can, immediately after they are released, act in autocrine or paracrine fashion and in contrast to the classical transmitters are not localized to specific synaptic sites. Since the gases may affect many cells in their vicinity this function has been called "volume signalling". Of course, this kind of signaling is not as punctual in targeting postsynaptic cells as it is the case with classical synaptic transmission and its action is highly dependent on the concentration gradient within the tissue. Volume signaling is particularly interesting in the brain where thousands or millions of synaptic contacts may be affected. The implication of such signals on nervous function and information processing in the central nervous system, however, remains to be investigated in detail.

In experiments using knockout animals it could be shown for all gasotransmitters that after elimination of appropriate enzymes the gases are no longer produced and the expected pathophysiological modifications developed,

i.e., metabolic or erectile dysfunctions, or high blood pressure. Since the book on "Signal Transduction and the Gasotransmitters: NO, CO, and H_2S in Biology and Medicine", has been issued by Rui Wang (2004) an impressive amount of data has been collected and a great wealth of further information is distributed in the literature. We have asked distinguished colleagues in the field to summarize and review important biological, pharmacological, and medical functions on gasotransmitters and their implications. The authors were asked in particular to critically review the literature from their point of view and to ask questions and even speculate on new vistas.

Ulrich Förstermann and Huige Li in their chapter "Nitric Oxide: Biological Synthesis and Functions" summarize principles of NO biosynthesis, regulatory mechanisms, and a large array of physiological and pathophysiological functions. NO, due to its highly reactive chemical nature, is also capable of destroying parasites and tumor cells; however, in high concentrations it exhibits a Janus face contributing to processes such as neurodegeneration, inflammation, and tissue damage.

Ashley Untereiner et al. describe in their chapter "The role of CO as a gasotransmitter in cardiovascular and metabolic regulation" the production, physiological functions, such as in proliferation and apoptosis, pathophysiological actions of CO, as in diabetes, vascular diseases, hypertension, atherosclerosis, or myocardial infarction. In their final sections they summarize cellular and molecular mechanisms of CO effects including ion channel and receptor signaling and discuss the interaction of CO with other gases.

Hideo Kimura in his chapter on "Physiological and pathophysiological functions of hydrogen sulfide", after introducing some basic properties and the amphipathic chemistry of H_2S, its free and bound conditions, describes some detection methods and the endogenous enzymatic production of the gas. Furthermore, physiological functions, such as synaptic modulation in the brain and in the retina, in smooth muscle relaxation, its cytoprotective and pathophysiological roles in particular in ethylmalonic encephalopathy, in Down's syndrome or in vascular dysfunctions, and some therapeutic implications are covered.

In the chapter by Hanjing Peng et al. on "Methods for detection of gasotransmitters" a great deal of chemical and technical details are summarized. Various new techniques and chemoprobes for measuring all three gases, their applicability to biological systems, and their advantages and limitations are discussed. Electrochemical measurements appear most sensitive and allow for determination of temporal concentration changes, whereas fluorescent probes are favorable for spatial monitoring in living cells.

Guzel Sitdikova and Andrey Zefirov specialized in their chapter "Gasotransmitters on the regulation of neuromuscular transmission". All three gases are produced in the central nervous system in response to neural excitation and modulate neurotransmitter release and are involved in the regulation of synaptic plasticity affecting pre- or postsynaptic sites by different mechanisms. The authors summarize the literature and present own data concerning the effects and

mechanisms of the transmitter gases in the peripheral nervous system focusing on neuromuscular synapses.

Finally, Anton Hermann et al. focus on "Ca^{2+} activated BK channel modulation by gasotransmitters". These ion channels, which are present in a large variety of cells and organs, are prominent targets of the gases. The structure and functions of these channels and their pharmacology and posttranslational modifications are described. BK channel modulation through gasotransmitters and their implication for physiology and pathophysiology are highlighted.

The advent of gasotransmitters has profoundly changed our way of thinking about biosynthesis, liberation, storage, and action mechanisms by cellular signaling. The gases will certainly play an increasingly important role to understand how cellular signaling is modulated and fine-tuned, particularly in the brain. The investigation of the interaction of NO, CO, and H_2S is still at its infancy! More knowledge is needed concerning the metabolic products of gasotransmitters, in particular of NO and H_2S, and the functions of some related molecules, such as nitrosonium cation (NO^+), which is isoelectronic with CO or the hyponitrite anion (NO^-). Future studies will have to probe into further details of their physiology, pathophysiology, and pharmacology. The development of drugs containing specific active ingredients with little or no side effects to manipulate the ana-/metabolism of gasotransmitters or their targets could be of an interesting and probably fruitful pharmacological task.

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