Chapter 1
Overview of the Carbonic Anhydrase Family

Robert McKenna and Susan C. Frost

Abstract The purpose of this collection of chapters is to provide a glimpse of where the carbonic anhydrase (CA) field is. This book is by no means fully inclusive, as only a few of the lead researchers around the world contributed; it serves only to show that the CA field is still pushing the boundaries of research as it has done since its discovery, and will do for a long time to come.

Keywords Carbonic anhydrase • Anhydrase family • Metalloenzymes • Structure • Function • Kinetics • Pathology • Biocatalyst • Ion transport • Acid-base balance • Regulation • Bicarbonate • CO_2 • Proton

The carbonic anhydrases (CAs; EC 4.2.1.1) are a family of metalloenzymes that catalyze the reversible hydration of carbon dioxide and bicarbonate. Since their discovery 80 years ago, in 1933, CAs have been at the forefront of scientific discovery; from the understanding of enzymatic reactions to structural biology, molecular dynamics, drug discovery and clinical medicine. The CAs are categorized into five distinct classes (α, β, γ, δ and ζ). The α-class is found primarily in vertebrates (the only class of CA in mammals). This class is also the most well characterized of the five classes. β-carbonic anhydrase is observed in higher plants and some prokaryotes, γ is present only in archaebacteria, whereas the δ and ζ classes have only been observed in diatoms. These classes of enzymes are distinct from each other in primary amino acid sequence and 3-D tertiary structure (α, β, γ),

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implying convergent evolution of a biochemical reaction essential for life processes. These ubiquitous enzymes equilibrate the reaction between three simple chemical molecules: CO_2, bicarbonate, and protons; hence, they have important roles in ion transport, acid–base regulation, gas exchange, photosynthesis, and CO_2 fixation. Furthermore, CAs are expressed variably in different species, tissues, and cellular compartments which differ in temperature, acid–base status and metabolic rate, that defined the contributions of catalyzed CO_2 reactions in many physiological processes. Drs. Robert McKenna and David Silverman, with colleagues Christopher Boone and Melissa Pinard, discuss the structure and mechanism of the α-carbonic anhydrases in Chap. 3; Dr. Roger Rowlett discusses the structure and function of the β-carbonic anhydrases in Chap. 4; Drs. Kumar and Ferry reveal the biology of the prokaryotic family of CAs in Chap. 5; and Dr. Matt Kimber describes the carboxysomal CAs in Chap. 6. Finally, Drs. Vincenzo Alterio, Simona Monti, and Giuseppina De Simone describe the thermal-stable CAs from a structural perspective in Chap. 19.

Multiple chapters are devoted to the α-class. By way of overview, Dr. Susan Frost describes the physiological significance of the catalytically active α class family in Chap. 2 while Drs. Ashok Aspatwar, Martti Tovanen, Csaba Ortutay, and Seppo Parkkila, describe the molecular biology and evolution of the "inactive" α class isoforms that are collectively called carbonic anhydrase related proteins or CARPs in Chap. 8. The importance of the α CAs in neuronal excitability is discussed by Drs. Eva Ruusuvuori and Kai Kaila in Chap. 14. Dr. Erik Swenson describes the impact of the α CAs on altitude sickness in Chap. 19. Multiple authors have contributed chapters on the membrane-associated CAs. Drs. William Sly and Abdul Waheed describe the history of the discovery of CA IV in Chap. 9. Specific emphasis is given to the tumor-associated CA IX by Dr. Egbert Oosterwijk in Chap. 10, Drs. Martin Benej, Silvia Pastorekova, and Jaromir Pastorek in Chap. 11, Drs. Narges Tafreshi Mark Lloyd, Marilyn Bui, Robert Gillies, and David Morse in Chap. 12, and Drs. Paul McDonald and Shoukat Dedhar in Chap. 13. The functional significance of these membrane associated CAs, in relation to acid–base transporters, is described in Chap. 7 by Drs. Holger Becker, Michael Klier, and Joachim Deitmer.

Inhibition of CAs has a long pharmacological history in many fields, being involved in various physiological reactions including respiration, pH regulation, Na^+ retention, calcification, tumorigenesis, electrolyte secretion, gluconeogenesis, ureagenesis, and lipogenesis. Hence CA inhibitors (CAIs) have long been used as systemic anticonvulsants, topically acting anti-glaucoma agents, and agents for treating altitude sickness, and have recently shown promising results as anti-obesity, anti-pain, and anti-tumor treatments. In addition to the treatment of human aliments, CAIs' uses are also emerging as anti-fungal and bacterial agents. The design of CA inhibitors is deliberated by Dr. Robert McKenna and Claudiu Supuran in Chap. 15 and identification of natural product inhibitors is discussed in Chap. 16 by Drs. Sally-Ann Poulsen and Rohan Davis. The application of these inhibitors are discussed by Drs. Andrea Scozzafava and Claudiu Supuran in Chap. 17 (glaucoma) and Dr. Erik Swenson in Chap. 18 (altitude sickness).

CAs have also been gaining industrial interest as bio-catalysts for carbon sequestration of flue-gas from coal-fired power plants and in exploiting CAs in algae as a way to capture CO_2 and convert it into biofuels or other valuable products. The favorable properties of CAs such as fast kinetics, easy expression, high solubility and intermediate heat resistance have made them an attractive candidate for numerous industrial and medical applications; for example, to aid in CO_2 gas exchange in artificial lungs. Drs. Zoë Fisher and Javier González discuss these issues in detail in Chap. 20.

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