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Joseph C. LaManna
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Oxygen Transport to Tissue XXXIX

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Preface

This volume is the publication of papers presented at the 44th annual meeting of the International Society on Oxygen Transport to Tissue, ISOTT, held in Chicago, IL, USA, from July 10 to July 14, 2016. I believe it represents a wonderful variety of perspectives focusing on a great deal of the areas of research on the transport of oxygen to tissues. The work presented has been subjected to peer review by the leading experts in this area. Through the review by members internationally recognized for their contribution to the field, the science therein is of the highest quality.

The meeting involved 105 scientists from 60 institutions in 15 countries from North America, Asia, and Europe. Given the busy schedules of many of the best-known participants, topics were spread throughout the meeting. In the best tradition of ISOTT, this allowed presentations and presenters to mingle with researchers from intellectually distant backgrounds. The exotic spice of new ideas was thereby mingled with the broth of established understanding to stimulate the true value of this meeting: innovation.

The meeting keynote presentation was given by Greg Semenza, who at the time had not yet won the Lasker Award for 2016, detailing the latest research on molecular biology of the required organismal response to low levels of local oxygenation. From molecular biology to individual human response, to oxygen changes monitored by optical/near-infrared spectroscopy/tomography, to novel electron resonance spectroscopy and spectroscopic imaging, to progress in blood substitute research, retinal physiology, etc., the quality and innovation of the research and those involved in it were outstanding and exciting. In-depth presentations from our internationally recognized experts accompanied wide-ranging shorter presentations. As in recent past meetings, poster information was communicated to the meeting attendees as a whole with succinct poster summary presentations that allowed our participants to focus on the novel, compelling the poster sessions.

In addition to the presentation of science, the history of ISOTT has revolved about the opportunities that the meeting and its venue provided for productive scientific exchange between attendees. The location of the meeting at a boutique in the heart of Chicago's Miracle Mile provided relaxed access to the most diverse restaurants, from small inexpensive but high-quality quiet venues to some of the finest in the world. Here, in-depth discussions could extend into the evening free of constraint. The history of the city, considered by many to be the architectural capital of the USA, was elucidated during the Chicago River tour. The vistas provided by the 95th floor banquet, the weather performance of a July storm with its second-order (and perhaps third-order) rainbow after dinner, and the city fireworks that followed gave the muscular sense of one of America's signature cities. This seemed a superb setting for the optimum exchange of science and the engendered friendship.

We acknowledge the excellent support of the members of the Department of Radiation and Cellular Oncology including Mert Vincent, Matthew Maggio, Emily Toops, Eugene Barth, Richard Miller, and Feya Epel for help in the preparation of the meeting materials and for ensuring the smooth running of the meeting. Our ISOTT treasurer, Dr. Peter Keipert, provided financial wisdom through the preparative stages of the meeting. Members of our Local Organizing Committee, our Scientific Committee, the ISOTT Executive Board, and the session chairs and cochairs burnished the roster of presenters and disciplined our exciting sessions. Those who presented at the meeting need our particular gratitude for insight at the heart of the meeting. We thank those of our participants who submitted their work as scientific publications. We especially thank our reviewers of the submitted papers who provided wisdom and insight without which the meeting would not have been such a success and the papers which have issued in this volume so important.

Chicago, IL, USA

Boris Epel
Howard J. Halpern

Acknowledgments

As president of the 2016 Meeting of the International Society on Oxygen Transport to Tissue, held on July 10–14, 2016, in Chicago, USA, I would like to gratefully acknowledge the support of our sponsors.

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July 10–14, 2016, Chicago, IL

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The Melvin H. Knisely Award

The Melvin H. Knisely Award was established in 1983 to honor Dr. Knisely's accomplishments in the field of the transport of oxygen and other metabolites and anabolites in the human body. Over the years, he has inspired many young investigators, and this award is to honor his enthusiasm for assisting and encouraging young scientists and engineers in various disciplines. The award is to acknowledge outstanding young investigators. This award was first presented during the banquet of the 1983 annual conference of ISOTT in Ruston, Louisiana. The award includes a Melvin H. Knisely plaque and a cash prize.

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The Dietrich W. Lübbers Award

The Dietrich W. Lübbers Award was established in honor of Professor Lübbers's long-standing commitment, interest, and contributions to the problems of oxygen transport to tissue and to the society. This award was first presented in 1994 during the annual conference of ISOTT in Istanbul, Turkey.

Dietrich W. Lübbers Award Recipients

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The Britton Chance Award

The Britton Chance Award was established in honor of Professor Chance's long-standing commitment, interest, and contributions to the science and engineering aspects of oxygen transport to tissue and to the society. This award was first presented in 2004 during the annual conference of ISOTT in Bari, Italy.

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The Duane F. Bruley Travel Awards

The Duane F. Bruley Travel Awards were established in 2003 and first presented by ISOTT at the 2004 annual conference in Bari, Italy. This award was created to provide travel funds for student researchers in all aspects of areas of oxygen transport to tissue. The awards signify Dr. Bruley's interest in encouraging and supporting young researchers to maintain the image and quality of research associated with the society. As a cofounder of ISOTT in 1973, Dr. Bruley emphasizes cross-disciplinary research among basic scientists, engineers, medical scientists, and clinicians. His pioneering work constructing mathematical models for oxygen and other anabolite/metabolite transports in the microcirculation, employing computer solutions, was the first to consider system nonlinearities and time dependence, including multidimensional diffusion, convection, and reaction kinetics. It is hoped that receiving the Duane F. Bruley Travel Award will inspire students to excel in their research and will assist in securing future leadership for ISOTT.

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2004 Helga Blocks (Belgium), Jennifer Caddick (UK), Charlotte Ives (UK), Nicholas Lintell (Australia), Leonardo Mottola (Italy), Samin Rezania (USA/Iran), Ilias Tachtsidis (UK), Liang Tang (USA/China), Iyichi Sonoro (Japan), Antonio Franco (Italy)

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2009 Lei Gao (UK), Jianting Wang (USA), Obinna Ndubuizu (USA), Joke Vanderhaegen (Belgium)

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Kovach Lecture

The Kovach Lecture is presented periodically to honor a career dedicated to oxygenation research. Arisztid Kovach was a world-renowned cardiovascular physiologist and one of the early leaders of ISOTT. This lecture is dedicated to his remarkable scientific and teaching career.

Kovach Lecture Recipients

2011 John Severinghaus
2012 Peter Vaupel
2013 No Recipient
2014 Edwin Nemoto
2015 No Recipient
2016 No Recipient

Contents

Part I
Cell Metabolism, Tissue Oxygenation and Treatment

Chapter 1
Oxygen Sensing by the Carotid Body: Past and Present

Nanduri R. Prabhakar and Ying-Jie Peng

Abstract It is now well established that carotid bodies are sensory organs for monitoring arterial blood oxygen levels and trigger reflexes that are critical for maintaining homeostasis during hypoxemia. This review article provides a brief account of the early studies leading to the discovery of the carotid body as a sensory receptor and addresses current views of O_2 sensing mechanism(s) in the carotid body and their physiological importance.

Keywords Gasotransmitters • Carbon monoxide • H_2S • Hypoxia • Ion channels

1 Introduction

The carotid body (also called *glomus caroticum*) is a small organ located at the bifurcation of the internal and external carotid artery. The discovery of carotid body as a sensory organ for detecting arterial blood O_2 levels opened a new area in physiology. This review article provides a brief account of the history of the discovery of the carotid body as a sensory organ and current concepts of O_2 sensing by the carotid body. A detailed account of the history of discovery of the carotid body and advances in carotid body physiology can be found in recent review articles [1, 2].

2 Discovery of Carotid Bodies as an O_2 Sensing Organ

Pflüger, a German physiologist, as early as 1868, reported that hypoxia stimulates breathing [3]. This finding spurred investigations to identify the structures that "sense" systemic O_2 levels and trigger physiological responses. Although studies between the 18th and 20th centuries identified a structure resembling "ganglion"

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[4], or a "gland" [5] at the bifurcation of the common carotid artery, no physiological function was assigned to this organ.

Fernando de Castro at the Cajal Institute, Madrid, Spain, showed that the carotid body is a complex structure comprised of small blood vessels, axons of the sympathetic nerves, glandular cells which were innervated by glossopharyngeal nerve fibers. He concluded that the carotid sinus nerve innervating the carotid body is sensory in nature and glomus cells are of secretory phenotype, and proposed that the carotid body detects the chemical composition of arterial blood i.e., chemical sensing, and that the information is transmitted to the nerve terminals [6–10].

In the 1920s, Jean-Francois Heymans and Corneille Heymans in Belgium, while studying reflex regulation of blood pressure from the sino-aortic region, found that hypoxia-induced stimulation of breathing was abolished after sectioning carotid sinus nerves. Their studies led to the proposal that the carotid sinus was the seat of pressor receptors, and the chemical composition of arterial blood is sensed by the carotid body [11–18]. Thus, both Fernando De Castro and Heymans' group independently discovered the sensory nature of the carotid body. Cornielle Heymans was awarded the Nobel Prize in Physiology & Medicine in 1938 and he was nominated by the Hungarian Professor Mansfeld. Unfortunately, nobody nominated De Castro for the Nobel Prize. However, the Nobel Citation duly acknowledged the contributions of Fernando De Castro [1].

Between 1930 and 1939, three groups of investigators including G. Stella from Padova, Italy, Pierre Rijlants, Ghent, Belgium, Y. Zotterman, G. Lilljestrand, and U.S. von Euler in Stockholm, independently recorded the electrical activity from the carotid sinus nerve [19]. These studies showed that asphyxia, hypoxia and hypercapnia, all increased carotid body sensory nerve activity. The study by von Euler et al. [20] further established stimulus-response of the carotid body response to hypoxia and CO_2.

A prevailing view in the 1930s was that brain senses the chemical composition of arterial blood and evokes physiological responses. Consequently, many physiologists doubted the theory that the carotid body is a sensory organ for monitoring arterial blood gas composition. Corneille Heymans, shortly after the discovery of the carotid body function, joined the Western Reserve University in Cleveland to work with Carl Wiggers, a renowned physiologist, who made seminal contributions to cardiovascular physiology. Upon hearing C.F. Heymans' discovery of the sensory nature of the carotid body, Wiggers commented that "no text book ever said that". However, Wiggers arranged an experiment for Heymans to prove his claim about the sensory function of the carotid body. Heymans demonstrated hypoxia-induced hyperventilation was abolished after bilateral ablation of carotid sinus nerves. Seeing this experiment, Wiggers commented "Yes…. The dog is right … and text books are wrong". Goran Liljestrand, who was Professor of Physiology at Karolinska Institute, Stockholm also doubted the theory of chemical sensing by the carotid body. In 1935, Zotterman presented recordings of the carotid body sensory activity at the Physiological Society meeting in Stockholm, and Liljestrand gave up his opposition and joined Zotterman and Ulf von Euler in the experiments characterizing the carotid body sensory nerve response to hypoxia and CO_2, which were published in 1939 [20]. In 1940, Henderson at Yale listened to Zottermans' gramophone recordings of the carotid body sensory nerve activity and – he too gave up his opposition. Carl F. Schmitt in Philadelphia, however, did not give up his resistance until 1959. However, he subsequently withdrew his opposition at the Montreal International Congress of Physiology [19].

3 Current Views on Carotid Body O_2 Sensing

A substantial body of evidence accumulated during the subsequent years suggests that glomus cells are the primary site of transduction and they work in concert with the nearby afferent nerve ending as a "sensory unit" [2]. Much attention has been focused on delineating the mechanism(s) of hypoxic sensing by the carotid body and identifying the potential O_2 sensor. Given that the carotid body responds to hypoxia within a few seconds, it is likely that the transduction process involves changes in existing proteins rather than *de novo* protein synthesis [21].

Emerging evidence in the past few years suggests that hypoxic sensing by the carotid body chemoreceptor utilizes biochemical mechanisms involving O_2-dependent interplay between two gaseous messengers, carbon monoxide (CO) and hydrogen sulfide (H_2S). CO is generated during the enzymatic degradation of heme by heme oxygenases 1 and 2(HO-1and HO-2) [22]. HO-1 is an inducible isoform and HO-2 is constitutively expressed in various tissues, including the carotid body [23–25]. HO-2 is the primary enzyme contributing to CO generation in the carotid body [26]. Hypoxia leads to a graded reduction of CO levels in the carotid body [27], suggesting that CO generation from HO-2 is sensitive to changes in O_2. The inherent O_2 sensitivity of HO-2 requires two cysteine residues (Cys^{265}, and Cys^{282}) in the heme regulatory motif [26]. With intact Cys^{265} and Cys^{282} residues, HO-2 exhibits low affinity for O_2 ($K_m = 65 \pm 5$ mmHg), whereas mutation of Cys^{265} and Cys^{282} dramatically increases O_2 affinity ($K_m = 25 \pm 3$ mmHg). Physiological studies showed that CO signaling during normoxia inhibits CSN activity [25, 27].

Under hypoxic conditions, CO-dependent inhibition is released, leading to carotid body activation. CO mediates carotid body activation by increasing the synthesis of H_2S. Glomus cells express cystathionine-γ-lyase (CSE), an enzyme that catalyzes H_2S generation [28, 29]. Hypoxia increases H_2S generation in the carotid body in a graded manner, and this response is markedly attenuated or absent following pharmacological blockade or genetic ablation of CSE activity [28]. However, the increased H_2S generation is not due to a direct effect of hypoxia on CSE, rather it is due to reduced CO levels and the resulting decrease in protein kinase G (PKG)-dependent phosphorylation of CSE (Fig. 1.1). Carotid body activation by hypoxia is severely impaired with genetic or pharmacological blockade of CSE [28], suggesting that CSE-derived H_2S mediates increased carotid body sensory nerve activity by hypoxia.

How might H_2S stimulate the carotid body sensory nerve activity? The current consensus is that hypoxia depolarizes glomus cells leading to Ca^{2+}-dependent

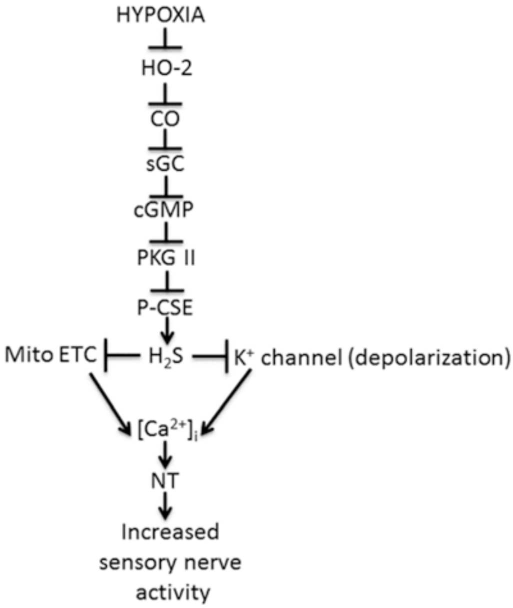

Fig. 1.1 The O_2 sensing and signaling pathway in the carotid body. Schematic presentation of CO-regulated H_2S generation in glomus cells of the carotid body and its impact on sensory nerve activity. *HO-2* heme oxygenase 2, *CO* carbon monoxide, *sGC* soluble guanylate cyclase, *cGMP* cyclic gunosine monophosphate, *PKG- II* protein kinase G-II, *P-CSE* phosphorylated cystathionine-ϒ-lyase, *Mito ETC* mitochondrial electron transport chain, *H_2S* hydrogen sulfide, *$[Ca^{2+}]_i$* intracellular calcium concentration, *NT* neurotransmitter

release of excitatory neurotransmitters, which by stimulating the afferent nerve ending increase carotid sinus nerve activity [2]. Consistent with this possibility, H_2S depolarizes glomus cells, which appears to be in part due to inhibition of either a TASK-like K^+ conductance [30], or inhibition of Ca^{2+}-activated K^+ channel activity [29, 31]. H_2S increases $[Ca^{2+}]_i$ in glomus cells and hypoxia-induced transmitter secretion is nearly absent in CSE –null glomus cells [32]. In addition, H_2S might act on mitochondrial electron transport chain glomus cells [30] (Fig. 1.1).

4 Physiological Implications of Carotid Body O_2 Sensing by Gasotransmitters

The chemosensory reflex is a critical regulator of autonomic functions [2]. A recent study examined the importance of gaso transmitter signaling in the carotid bodies in Spontaneous Hypertensive (SH), Brown Norway (BN), and Sprague-Dawley (SD) rats [27]. Compared to SD rats, SH rats displayed *augmented* and BN rats *attenuated* carotid body responses to hypoxia. The exaggerated chemosensory response in SH rats was associated with elevated basal and hypoxia-induced H_2S levels and markedly reduced CO levels in the carotid body. Treating SH rats, with L-propargylglycine (L-PAG), an inhibitor of CSE, or with CORM-2, a CO donor, eliminated hypersensitivity of the carotid body to hypoxia. Remarkably, L-PAG treatment markedly reduced the magnitude of hypertension in SH rats, suggesting