

Advances in Experimental Medicine and Biology 1071

Estelle B. Gauda · Maria Emilia Monteiro
Nanduri Prabhakar · Christopher Wyatt
Harold D. Schultz *Editors*

Arterial Chemoreceptors

New Directions and Translational Perspectives

 Springer

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Preface

What a pleasure it was for Dr. Machiko Shirahata and I to host the XXth International Society for Arterial Chemoreceptors at Johns Hopkins University in Baltimore, Maryland, from July 23 to 27, 2017. The theme of the meeting was “Making Sense Out of Sensing Hypoxia, New Directions and Translational Perspectives Across the Lifespan.” It was a wonderful reunion of friends and colleagues from 11 countries and 4 continents who came together to share their love for science and discovery connected by the carotid body. This book is the compilation of the science that was presented, a historical overview of ISAC meetings, by Dr. Robert Fitzgerald, and tributes to Dr. Machiko Shirahata, by Dr. James Sham, and Dr. Constancio Gonzalez by Dr. Nanduri Prabahakar, two giants in the field who had passed away since the last ISAC meeting in Leeds, in 2014. We are grateful to Springer for again helping us catalogue the events of the week, binding them together to join the other volumes on the shelf that have documented communications presented at the ISAC meetings since 1950, and thus the evolution of our understanding of how arterial chemoreceptors contribute to health and disease. In this volume the chapters cover chemoreception (peripheral and central) and mechanisms of O₂ sensing, embracing a variety of clinical-related issues including hypertension, obstructive sleep apnea, sudden infant death syndrome, obesity, heart failure, and the translational connection between laboratory science and clinical application. I encourage you to read the chapter “ISAC Historical Overview” by Dr. Robert Fitzgerald who chronicles the major contributions from each of the meetings since 1950.

There are many individuals who I have to thank for making the meeting a success. I had amazing talented and hardworking organizing and scientific committees. Rosie Silva, my administrative assistant at Hopkins who was the Senior Administrative Coordinator for the ISAC, effortlessly kept everything together (including me) and remembered every little detail to ensure the meeting ran smoothly and our guests felt welcomed. Without her attention to detail, I could not have moved to another country and started a new job 5 months prior to the meeting and pulled it off. I am also grateful to Sonia Dos Santos, the lead administrative assistant at SickKids. She orchestrated my seamless transition to a new country and job at SickKids, assisted in putting together the ISAC program, was able to come to the meeting to help Rosie, and meet all the wonderful people I had spoken about so fondly. I also knew she would be able to easily connect with the Portuguese group since she is also Portuguese. With Rosie and Sonia bookending the event not much

could go wrong. Machiko and I had several friends who volunteered their ideas, energy, and time, and I cannot thank them more. Santokh (Sam) Singh, a very good friend, my personal trainer in Baltimore, former real-estate agent for high-end condos in Baltimore, led the negotiations for the hotels, organized the trip to Annapolis, and visited the venues. Setsuko Takase, a very close friend of Machiko's who many of the ISAC members met in Leeds, is a travel agent and assisted many Japanese in organizing their visit or move to Baltimore. With her flare for elegance and exceptional good taste, Setsuko helped select the social venues. I especially appreciated all the help from George Kim, MD, ISAC Webmaster, who updated the website: carotidbody.org, and orchestrated all the electronic communications; he was invaluable. He also updated the ISAC members list with accurate contact information. I have known George throughout my career at Johns Hopkins and he too has been a close friend.

Although Dr. Machiko Shirahata passed away in April 2016, she made significant contributions to the organization of the meeting. Soon after the Leeds meeting, we met on multiple occasions over tea, wine, and sushi to talk about venues, potential funding sources for the meeting, and her legacy. Drs. Nanduri Prabahakar, Chris Wyatt, and Harold Schultz, members of the scientific committee and the selection committee for the Machiko Shirahata ISAC Trainee Travel Awards, were immensely helpful in creating the theme for the meeting "Making Sense Out of Sensing Hypoxia, New Directions and Translational Perspectives Across the Lifespan," selecting plenary speakers and organizing the sessions.

I would be remised if I did not take a moment to specially thank Dr. Nanduri Prabhakar for introducing me to the Carotid Body, allowing me to work in his laboratory when I was a Neonatology Fellow at Case Western University in 1989 when I only had a desire to understand and passion for learning and working hard, but no former training in research. He has mentored me throughout the years, always available for advice and encouragement (scientific, professional, and personal). He encouraged me to attend my first ISAC meeting in 1993, Dublin, Ireland, and submit an oral presentation (not a poster); little did I know then that I would become the first woman President of the ISAC Society in 2014. Thank you Nanduri for being such an amazing mentor, sponsor, and inspiration.

Dr. Machiko Shirahata was a dedicated scientist, wonderful mentor, and collaborator, had a love for life and travel, and was inspired by ISAC. Knowing that she had lung cancer, she reflected on how she might merge her passions by leaving a legacy. At the Leeds ISAC conference, she made a commitment to support young trainees and give them the opportunity to attend future ISAC conferences. To that end, through a generous donation from Machiko's estate made available to ISAC by her son, Akira Fitzgerald, 10 trainees received the Machiko Shirahata ISAC Trainee Travel Award to ISAC XX, and another 10 awards will be available for the 21st international conference in Lisbon, Portugal. Please refer to the chapter, Machiko tribute, written by Dr. James Sham for an overview of her life and contributions.

The Machiko Shirahata ISAC Trainee Travel Award compliments the Heymans-De Castro-Neil Awards which have been routinely given to two to

three trainees for the best abstracts presented by a trainee since 1989 at the X ISAC meeting.

These meetings always need sponsors, and we thank the Division of Neonatology at The Hospital for Sick Children, the Division of Neonatology at Johns Hopkins Hospital, *Journal of Physiology*, and Dr. Robert Fitzgerald for their generous donations.

I invite those who attended the conference and those who were unable to join us in Baltimore to take a moment to peruse the chapters in this book. True to the theme of the conference, the chapters outline new cutting edge research involving the carotid body and how oxygen is sensed across the lifespan and the translational implications of the work. The full length plenary communications presented by Drs. Greg Semena, Jan Marino (Nino) Ramirez, Christopher Wyatt, Jayasri Nanduri, Rodrigo Iturriaga, Michael Joyner, Andrea Porzionato, Patrice Guyenet, and Cormac Taylor will be published in an upcoming issue of the *Journal of Physiology*.

At the business meeting, Emilia Monteiro, was elected the President of ISAC and will host XXI ISAC meeting in Lisbon, Portugal, in 2020.

The ISAC meeting from the beginning was created on the solid premise of sharing ideas, collaborations, and discovery to explain basic human physiology. The collaboration between Dr. Fernando De Castro from Spain who performed the exquisite anatomical-histology of the carotid body and Dr. Heymans who performed the definitive experiments showing its role in chemoreceptor for which he won the Nobel Prize in 1938 (incomplete thought). They too met at scientific meetings, shared ideas, and collaborated on experiments. So I end this preface where it all began using a quote from the Swedish Professor, G Liljestrang in 1940, when the Nobel Prize was presented to Heymans for his characterization of “a curious structure” which was so beautifully identified and anatomically detailed by De Castro.

“Since the end of the eighteenth century we know of the existence of a curious structure in the region of the sinus, the glomus caroticum or carotid body which, in man, extends over only a few millimetres. The glomus consists of a small mass of very fine intertwining vessels arising from the internal carotid and enclosing various different types of cells. It has been considered by some as being a sort of endocrine gland similar to the medulla of the suprarenal glands. De Castro, however, in 1927 demonstrated that the anatomy of the glomus could in no way be compared to that of the suprarenal medulla. De Castro suggested rather that the glomus was an organ whose function was to react to variations in the composition of the blood, in other words an internal gustatory organ with special chemo-receptors.

In 1931, Bouckaert, Dautrebande, and Heymans undertook to find out whether these supposed chemo-receptors were responsible for the respiratory reflexes produced by modifications in the composition of the blood. By localized destruction in the sinus area they had been able to stop reflexes initiated by pressure changes, but respiratory reflexes could still continue to occur in answer to changes in the composition of the blood. Other experiments showed that Heymans’s concepts on the important role played by the glomus in the reflex control of respiration by the chemical composition of the blood were undoubtedly correct.”

Prof. G. Liljestrand (Karolinska Institutet); presentation of the 1938 Nobel Prize in Physiology of Medicine to Prof. C. Hyemans (Ghent, Belgium; January 16, 1940)

ISAC President, 2014–2017
Bethesda, MD, USA

Estelle B. Gauda, MD

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The History of the International Society of Arterial Chemoreception (ISAC)

At the conclusion of the 20th meeting (12th meeting of ISAC formally so constituted) in Baltimore, MD, USA, I was asked to write a history of ISAC. Being the last active founding member of ISAC, I thought the archives of ISAC should have some record of our scientific labors/successes regarding arterial chemoreception. Because of the goodness of Camillo Di Giulio, Chris Wyatt, Ronan O'Regan, and Keith Buckler, I received a listing of chemoreceptor meetings that predated those under the formal auspices of ISAC. ISAC was founded in a St. Louis restaurant after a FASEB meeting in 1987 by Carlos Eyzaguirre, Sal Fidone, Sukhamay Lahiri, Donald McDonald, and myself. ISAC members would like to see those initial/original meetings pre-dating ISAC included in this historical overview. And so they have been. We have a record of 20 such gatherings of which the final 12 are ISAC meetings.

With the data available, I have tried to be consistent in presenting the facts and the ambiance of each meeting at least briefly: the meeting's date, number, primary mover or ISAC president, title of volume containing presentations, editors of volume, location of publisher, publisher, date of publication, volume number in *Advances in Experimental Medicine and Biology*. There follows: location of meeting, number of presentations, and number of contributors to the presentations. And, finally, an effort was made to spell out some of the issues discussed and debated, or some other facets of the ambiance.

1950 Meeting I: Göran Liljestrand

Co-organizers of the first ISAC meeting were Ulf von Euler and Yngve Zotterman. Held in Stockholm, Sweden, in August 1950, the meeting did highlight three investigators who contributed to chemoreceptor studies for several years: Fernando De Castro, the primary originator of carotid body studies, Corneille Heymans who produced so much regarding the respiratory reflex effects of carotid/aortic area stimulation that he was awarded the Nobel Prize in Physiology or Medicine for 1938, and Eric Neil who focused on the circulation. De Castro's 1928 paper described the CB: "organe sensoriel special dedie a percevoir quelques modifications qualitative du sang, plutot que d'un appareil destine a recevoir les variations de la pression sanguine." He was the first to demonstrate with classical nerve studies the *sensory* nature of

the fibers abutting on the carotid body's type I cells and was the first to suggest the organ "tasted" the qualitative composition of the blood perfusing it. Heymans forcefully demonstrated that the hyperpnea consequent to hypoxia exposure was generated by peripheral chemoreceptors and not centrogenic. At that time CO₂-generated increases in ventilation needed more study. And Neil presented the role of the carotid bodies in the circulation especially during hemorrhage. He also spoke on autoregulation of the organ's blood flow. His ideas are found in the *Handbook of Physiology, Section 2: The Cardiovascular System, Volume III: Peripheral Circulation and Organ Blood Flow, Part 1*, Chapter I, "Peripheral blood flow: Historical aspects," pp. 1–20.

1966 Meeting II: Bob Torrance

Presentations are found in *Arterial Chemoreceptors*. Edited by R.W. Torrance. Oxford and Edinburgh, Blackwell Scientific Publications, 1968. These are the Proceedings of the Wates Foundation Symposium held at Oxford in July 1966. Bob's "Prolegomena" surveyed virtually all CB research up to that point. It is 40 pages long with 133 references and covers every facet of CB morphology, chemistry, neurophysiology, and systemic reflex responses. The earliest references to works of physiology appear to have been published in 1919 and 1922. Most come from the late 1940s, 1950s, and 1960s. To summarize the contents of this "Prolegomena" would be impossible. But for a young investigator interested in history and an understanding of the great work of earlier years, this would be a very worthwhile exercise. Thirty-four papers were presented by 50 investigators, but 70 attendees participated.

1973 Meeting III: Michael Purves

Presentations are found in *The Peripheral Arterial Chemoreceptors*. Edited by M.J. Purves. London/New York, Cambridge University Press, 1975. Bristol saw the presentation of 28 papers by 48 investigators of whom 35 participated in the meeting. Meant to afford opportunities for discussion of significant controversial data, the meeting was marked with a debated discussion of the existence, mechanisms, and functional significance of efferent inhibition of carotid body neural output. Donald McDonald and Bob Mitchell very elegantly presented ultrastructure of the organ and revealed the reciprocal synapses existing between the afferent fibers abutting on the type I cells of the organ. These fibers are the major type in the carotid sinus nerve. Eyzaguirre presented a reexplored version of De Castro's beautiful drawings of the carotid body. Of considerable interest to the investigators of ventilation control was the observation of Ponte and Purves that chemoreceptors should be relatively unresponsive to the oscillations of CO₂/H⁺, at least during normal breathing.