O_2/CO_2: Biological Detection to Homeostatic Control

1

Robert S. Fitzgerald

Abstract

Oxygen (O_2) and Carbon Dioxide (CO_2) are the two gases to be detected and controlled. Of interest might be a query of the evolutionary origin of each. From the cooling of the Big Bang (~13.8 Billion Years Ago [BYA]) came a quark-gluon plasma from which protons and neutrons emerged, producing H, He, Li. As H and He collapsed into the first stars at ~13.3 BYA carbon and monatomic oxygen were generated. Some 3 billion years ago greater amounts of diatomic oxygen (O_2) were provided by earth's photosynthesizing bacteria until earth's atmosphere had sufficient amounts to sustain the life processes of multicellular animals, and finally higher vertebrates. Origin of CO_2 is somewhat unclear, though it probably came from the erupting early volcanoes. Photosynthesis produced sugars with O_2 a waste product. Animal life took sugars and O_2 needed for life. Clearly, animal detection and control of each was critical. Many chapters involving great heroes describe phases involved in detecting each, both in the CNS and in peripheral detectors. The carotid body (CB) has played a crucial role in the detection of each. What reflex responses the stimulated CB generates, and the mechanisms as to how it does so have been a fascinating story over the last 1.5 centuries, but principally over the last 50 years. Explorations to detect these gases have proceeded from the organismal/system/ organ levels down to the sub-cell and genetic levels.

Keywords

Oxygen · Carbon dioxide · Great oxygen event · Chemoreceptors

1.1 Introduction

For the past 30 years the International Society for Arterial Chemoreception (ISAC) has addressed the issues of detecting O_2 and CO_2 in order to control them better for the homeostatic benefit of the organism. And even as far back as 1950 groups studying this have met quite frequently. To explore detection and homeostatic control of these gases immediately provokes two questions: How is this to be done? Why is it to be done? In the vertebrate the cardiopulmonary system is the tool which captures air from the external environment and delivers it to the cells of the organism, specifically to the mitochondria of the cells where the electron transport chain uses it as a last step in the oxidation of glucose. Is that important? And

R. S. Fitzgerald (✉)
Departments of Environmental Health & Engineering, of Physiology, of Medicine, The Johns Hopkins University Medical Institutions, Baltimore, MD, USA
e-mail: rfitzger@jhsph.edu

E. B. Gauda et al. (eds.), *Arterial Chemoreceptors*, Advances in Experimental Medicine and Biology 1071, https://doi.org/10.1007/978-3-319-91137-3_1

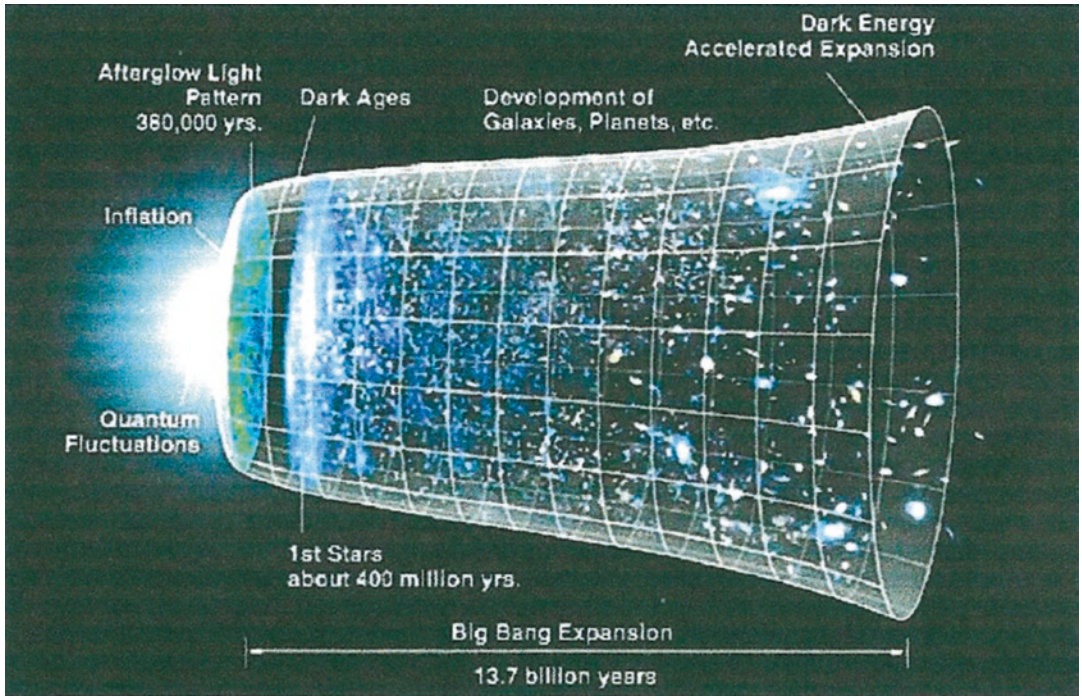

Fig. 1.1 Big bang. From hot quarks and an initial expansion the universe cooled, generating subatomic particles followed by simple atoms. Gravity brought these together to form the heavier atoms. Stars, galaxies were also formed. (From: Wikipedia, the Free Encyclopedia. Original version: NASA/WMAP Science Team, modified by Ryan Kaldan. With permission of JPL Image Use Policy)

if so, why? A homey experiment can give us a clue. How long can a subject hold her/his breath? Maybe 90 s would be an average duration.

So whereas one can go without food for a month, and without fluid for possiblly a week one needs air in seconds. The oxidation of glucose requires the air's oxygen (O_2) to generate ATP, the biological energy required for all the organism's living activities (e.g., heartbeat, diaphragm contracting, local motion, thinking). Mitochondria need O_2 in a hurry. Further, the metabolic resulting CO_2 and H_2O must be expelled. Hence it is clear the organism must be able to detect and control these two gases for life.

Since O_2 and CO_2 are so fundamental to life, one might initially query just what is the origin of these two gases on this planet. The standard model of the cosmos has space-time arising at the Big Bang ~13.8 billion years ago (BYA); monatomic oxygen (O) arose from the stars ~ 13.3 BYA. The Milky Way galaxy formed ~8.8 BYA. Earth finally appeared ~ 4.54 BYA. The only O on earth at that time was what had resulted from nuclear fusion, a very small amount (Fig. 1.1).

Cyanobacteria appeared ~2.5 BYA, and began to photosynthesize, the product of which was sugars. Their chloroplasts used sunshine, water, and CO_2. But from where did *this* CO_2 arise? It's really unclear, but many speculate it was a component of volcanic gas. The O generated by physicochemical fusion from smaller atoms and O_2 from primitive photosynthesis was chemically captured on earth by dissolved iron and organic matter in the sea. About 2.3 BYA The Great Oxidation Event occurred. At this point the oxygen sinks in the sea and on land had become saturated and O_2 began to accumulate in the atmosphere (Lane 2003) (Fig. 1.2).

The story of biological evolution from the primordial cell has been told many times. And many air-breathers have preceded *homo sapiens*.

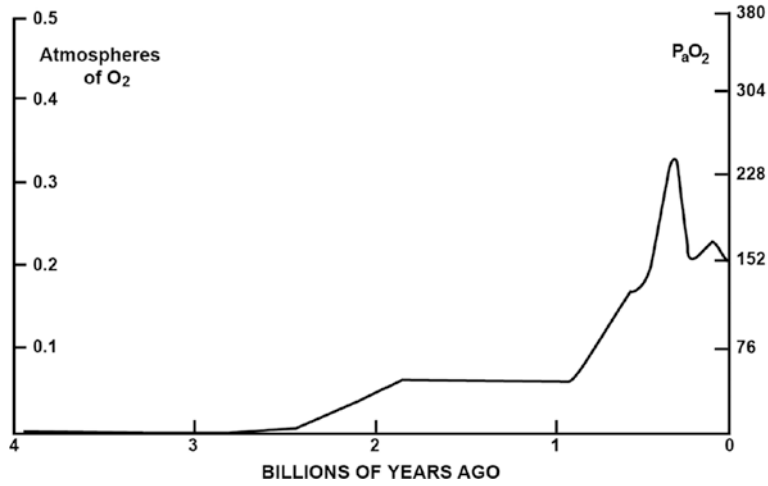

Fig. 1.2 Great oxygen event. From a virtually oxygen-free planet cyanobacteria began to produce O_2 as a waste product of photosynthesis about 2.5×10^9 years ago. But most was being absorbed into the oceans and seabed rock. With the saturation of these, about 1.85×10^9 years ago O_2 is becoming absorbed on land surfaces. About 850×10^6 years ago Earth's atmosphere starts to gain O_2. (Adapted from Wikipedia. Source: Holland, H [2006]. *Phil Trans Roy Soc: Biol Sci* 361: 903–915 with permission via Copyright Clearance Center)

However, this chapter will confine itself to how human subjects explored the issue of the biological detection of organismal O_2 and CO_2 in order to maintain homeostasis.

1.2 Oxygen/Carbon Dioxide and Respiration

The first method of biological detection was to observe general breathing movements, and later,the duration of breathing in an animal confined to a closed chamber. Parallel to this was the extinction of a flame or its effulgence in the same chamber.

But among the ancients of what was to become the European or western scientific tradition there was much ignorance concerning how the lungs and heart worked mechanically, and what each did for the organism. Plato thought breathing was involved in heat regulation, a balancing of the body's inner heat with the outside. Aristotle thought the arteries carried air, making the function of breathing unclear. Galen (131–201) also thought that since the heart drew air from the lungs and put it in the left ventricle breathing was meant to cool the blood. Most of the early, subsequent efforts to understand breathing were based on Galen's views. However, from the Arabic/Islamic medical/scientific traditions came the five volume *Canon of Medicine* in 1025 by the Persian philosopher Avicenna (980–1037) at age 21. The *Canon* brings together the successes of Hippocrates, Galen, as well as Egyptian, Persian, and Indian medical men plus his own research results and discoveries. The book was translated from Arabic into Latin and remained a text book or required background literature well into eighteenth century Europe. William Osler of McGill, Penn, and Hopkins fame described the *Canon* as "the most famous medical textbook ever written." Though a historical treasure, it is highly unlikely that detection of O_2 and CO_2 was ever considered. But Ibn-al Nafis (1213–1288), a second Arab physician and polymath deserves mention not for any work on the detection of O_2 and CO_2, but because his work on the pulmonary circulation, essential for rendering O_2 and CO_2 detectable, is the first. This is his description:

> *Blood from the right chamber of the heart must arrive at the left chamber, but there is no direct pathway between them. The thick septum of the*

heart is not perforated and does not have visible pores as some people thought or invisible pores as Galen thought. The blood from the right chamber must flow through the vena arteriosa (pulmonary artery) to the lungs, spread through its substances, be mingled there with air, pass through the arteria venosa (pulmonary vein) to reach the left chamber of the heart, and there form the vital spirit.

Ibn-al Nafis also commented on Avicenna's *Canon*. But we are unaware of any evidence supporting his thoughts on the detection of O_2 and CO_2. Although many important studies of the cardiopulmonary system's anatomy appeared in the first centuries of the second millenium (Leonardo de Vinci [1452–1519]), it would be safe to say none of them addressed the issue of the integrative control of oxygen & carbon dioxide homeostasis, or the organism's detection of these gases.

Robert Boyle (1627–1691) is thought to have performed the "fundamental experiment in the physiology of respiration". He recorded death in a variety of animals when they were enclosed in a chamber and the chamber evacuated. But if air was readmitted, they could be resuscitated. The chamber was designed and built by his colleague, Robert Hooke (1635–1703). An earlier version of this experiment was done by Leonardo da Vinci (1452–1519). On November 2, 1664 Hooke made holes in the lung of an anesthetized dog and passed air through the perforated lung. The dog remained alive, demonstrating it was air and not lung movement that was the essential contribution of the lung. Further, dark blood became red in the process. Richard Lower (1631–1691) had shown the same thing somewhat earlier. John Mayow (1643–1679) believed his observations led him to conclude that the "nitro-aerial particles with which spirit abounds" in air combined with the blood in the lung (like Ibn-al Nafis) in order to combine with combustible particles in the body. And though Mayow's best contributions are, perhaps, those he made regarding respiratory mechanics, there are historians who believe that Lavoisier (1743–1779) never cited the works of Mayow regarding respiratory chemistry of which he made significant use. Priestley's experiment on August 8, 1774 was to put an adult mouse in a chamber into which he had put the air he had gathered from buring *mercurius calcinatus* (HgO, mercuric oxide). He said if he had put the mouse into the chamber with common air, the mouse would have lasted only 15 min; but this mouse lasted a full hour. He did several more similar experiments. Priestley and Lavoisier were rivals. It seems probable that the former discovered what was to be called oxygen before the latter did. However, Lavoisier was a much more systematic investigator who organized both his own discoveries and those of Priestley into the complete oxygen story. Lavoisier is often called the Father of Modern Chemistry for his systematic thinking. He also was continually integrating oxygen with respiration. As a matter of fact Carl Scheele, a Swedish apothecary, discovered oxygen from his own studies before either Priestley or Lavoisier, but did not publish his discoveries until 1777. So by the end of the eighteenth century the need for oxygen (dephlogisticated air) in respiration was established quite firmly. Lavoisier is often criticized because he most often did not credit his predecessors. He did make an interesting discovery by recording oxygen consumption and CO_2 production over a 24 h period. O_2: 526 cc/min; CO_2: 204 cc/min, a RQ of 3.89, quite abnormal but possibly due to the measuring equipment at the time.

In addition to Lavoisier's awareness of CO_2 the Scotsman Joseph Black (1728–1799) made the close connection between CO_2 and the expirate in breathing, and found that CO_2 would not support either combustion or respiration. Finally, Daniel Rutherford (1749–1819) published in 1772 his report that once Black's "fixed air" (carbon dioxide) was removed from the expirate, a large amount of air remained which rapidly extinguished both life and flame. What remained was nitrogen. Henry Cavendish (1731–1810) also contributed to the discovery of nitrogen. By the end of the eighteenth century all respiratory-related gases had been detected and identified. The question remained as to *where* and *how* these gases were detected in the organism. But respiration (i.e., breathing) remained the method of detecting O_2 and CO_2 (Fig. 1.3).

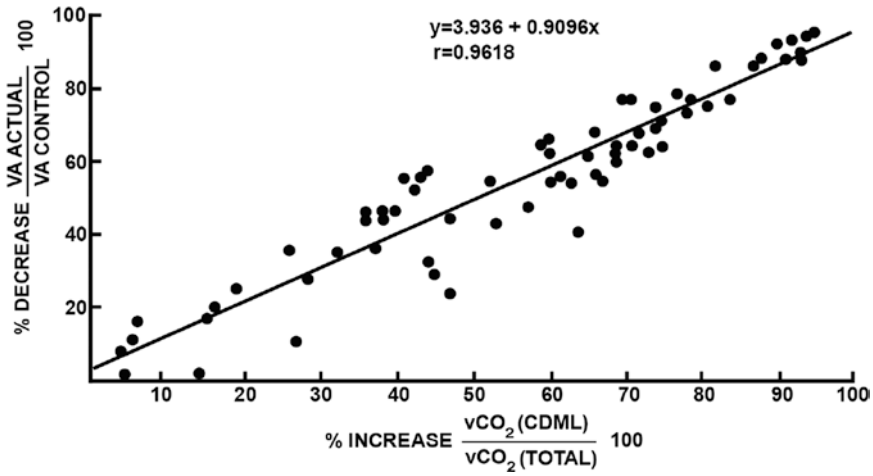

Fig. 1.3 Centrality of CO_2 on ventilation. In animal studies T. Kolobow used a device he called a "carbon dioxide membrane lung" (CDML) inserted into the venous circulation to scrub CO_2 from blood entering the right heart. Oxygen was supplied via a tracheostomy. The graph shows that of the total CO_2, the more of it scrubbed out by the CDML (abscissa), the more the alveolar ventilation decreased (ordinate) down to zero. (Kolobow et al. 1977; with permission Wolters Kluwer Health, Inc.)

1.3 CO_2 – Detecting Elements in the Respiratory System

What are the biological elements which will detect CO_2 and account for the cellular and integrative control of this gas to maintain homeostasis? In the absence of control, CO_2 could rise, as it does in obstructive sleep apnea, or in some cases of COPD. Respiratory acidosis develops. Any form of acute respiratory acidosis stimulates increases in both respiratory frequency and tidal volume. Further, it can impair the operation of both structural and functional proteins. Skeletal muscle (e.g., the diaphragm) decreases its force of contraction. Lowering CO_2 (respiratory alkalosis) results when ventilation exceeds metabolism. This can produce hypopnea, and eventually hypoxemia.

1.3.1 Detection in the CNS

In 1857 Kussmal and Tenner occluded the cerebral vasculature of an anesthetized dog. They observed the blood became dark; the dog hyperventilated, gasped, and eventually died (Kussmaul and Tenner 1857). This clearly suggested that CO_2 and hypoxia acted in the head. In 1885 Meischer-Rusch concluded from his experiments with human subjects (1885) that increases in ~~CO_2~~ was the ordinary stimulus to ventilation and not hypoxia since a small increase in CO_2 (1%) increased ventilation whereas a larger decrease in oxygen (3%) did not. The last decade of the nineteenth century saw the cross perfusion experiments in dogs by Leon Fredericq (1851–1935) in which he connected the proximal carotid arteries and jugular veins of Dog #1 to the distal counterparts in Dog #2; he then connected the proximals of Dog #2 to the distals of Dog #1. Occluding the trachea of Dog #1 increased the ventilation of Dog #2; this produced hypopnea and apnea in Dog 1. Further, hyperventilating Dog #1 made Dog #2 breathe less because he was receiving the depressed $PaCO_2$ from Dog #1. Using hyperoxia in other experiments with this preparation, Fredericq concluded to the landmark understanding for his day where and how CO_2 and O_2 influenced respiration (Fredericq 1890).

Working with human subjects, John Scott Haldane (1860–1936) once again demonstrated the power of CO_2 on ventilation. In human subjects a 3% rise in inspired CO_2 produced an increase in ventilation that could be matched only

by a 7% reduction in inspired O_2. And from his work with colleague John Priestley in miners and divers, they concluded that CO_2 was acting on respiratory centers in the head in normal breathing (Haldane and Priestley 1905). To what were the respiratory centers responding? Was it CO_2 or H ion? In 1911 the first of Hans Winterstein's "reaction theories" was proposed based on injections of fixed acid into his dogs (Winterstein 1911). But an unrelated experiment showed that CO_2 could diffuse from an extracellular space to an intracellular space whereas H ion did not (Jacobs 1920). So the increase in *blood* [H ion] from increased $PaCO_2$ was not the stimulus to the respiratory centers. Winterstein's 1921 "reaction theory" proposed that it was [H ion] in the respiratory centers which increased ventilation upon exposure to increased inspired CO_2 (Winterstein 1921).

Now the question arose as to just *where* in the head were these respiratory centers which were to control CO_2 homeostasis? In the late 19th and very early twentieth centuries hypoxia was thought to act centrally, perhaps even at the same receptors, by virtue of the lactic acid hypoxia generated. In 1954 Leusen seems to have further defined this locus of the "centers" to some place in or near the ventricles with his ventriculocisternal perfusion of fluid containing increased [H ion]. This work (Leusen 1954) certainly influenced the subsequent studies of Hans Loeschcke, Robert Mitchell and their colleagues (Loeschcke et al. 1953; Mitchell et al. 1963) who yet further defined the locus to the floor of the fourth ventricle of the medulla in cats. From their studies the sensitive centers were located on the ventral surface, quite superficially (Fig. 1.4).

However, the simultaneous studies of Pappenheimer, Fencl, and colleagues perfusing the brains of unanesthetized goats with mock CSF placed the sensitive "centers" about two-thirds to three-fourths the distance along a bicarbonate concentration gradient from the CSF to the blood (Pappenheimer et al. 1965). In 1982 Dempsey and Forster reviewed with extraordinary comprehension the work of Loeschcke and his colleagues as well as that of Pappenheimer and his colleagues plus their own work (the Madison, Wisconsin Group) involving many species, conditions, and experiments. They con-

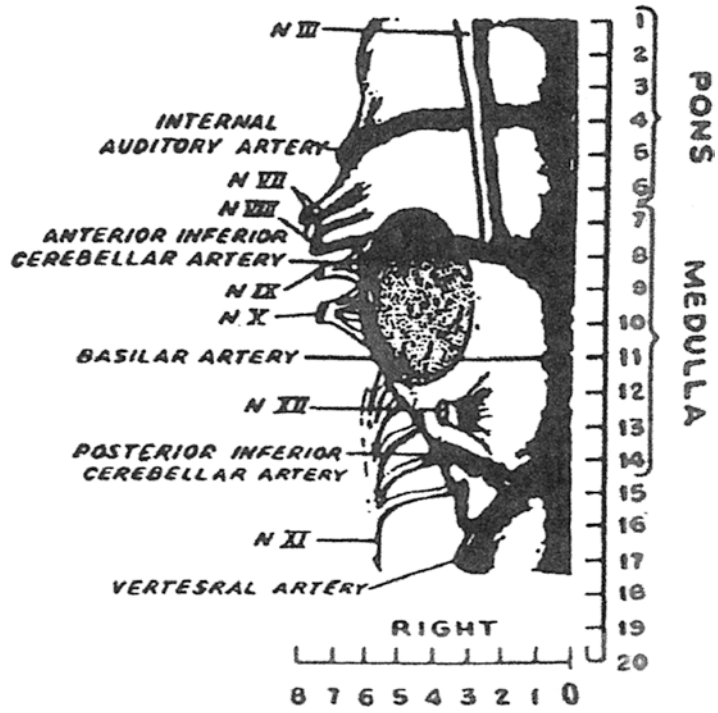

Fig. 1.4 CO_2-sensitive medullary areas. Ventral surface of the cat brain showing the areas to which Mitchell, Loeschcke, Severinghaus, and their colleagues applied CO_2/H^+ – soaked cotton pledgets to provoke an increase in ventilation, narrowing an important area for the biological detection of CO_2. (Mitchell et al. 1963; with permission Rightslink/John Wiley and Sons)

cluded that interstitial [H^+] was the stimulus for the medullary processes involved in the homeostatic control of ventilation in acid-base disturbances. And this area was also involved in eupneic breathing. But this [H^+]-sensitive structure was not on the surface but about 200 um below the ventrolateral surface of the medulla – closer to the interstitial fluid spaces (Dempsey and Forster 1982). At what is perhaps the molecular level for the biological detection of CO_2 Nattie has produced data showing that blocking an imidazole-histidine protein moiety in the ventrolateral medulla of in vivo preparation inhibits CO_2 sensitivity (Nattie 1995). But in more recent years efforts to identify CNS components of CO_2 detection met a problem. At a much more reduced level of organismal organization in the CNS our focus came to a specific location and on specific neurons and how these entities are to be challenged with the CO_2/H^+. Cells from the Phox2B retrotrapazoid nucleus, 5HT neurons of the medullary raphe, noradrenergic neurons of the locus ceruleus, and NK1R-ir cells of the raphe magnus…all are affected by CO_2/H^+, Excitation at a single site is modulated by subsequent hypocapnnic inhibition at other sites. And according to this long-term contributor to this controversy: central chemoreception is a distributed property; there is no unique chemoreceptor site nor is there a unique neuronal phenotype or mechanism" (Nattie and Li 2006). This information is interesting and helpful, but clearly indicates that more research is needed to clarify the picture of CO_2/H detection in the CNS.

1.3.2 Detection by the Carotid Body

Respiratory acidosis or metabolic acidosis according to one group is detected in an identical fashion. Both lower glomus cell pH (pH_i). This activates a $Na^{+/}H^+$ exchanger. H^+ is extruded bringing in Na^+. This activates and reverses the normal direction of the Na^+/Ca^{++} exchanger. Na^+ is extruded and Ca^{++} enters and attaches to the neurotransmitter-containing vesicles. The vesicles exocytose their contents into the synaptic cleft onto the appropriate post-synaptic receptors on the abutting afferent neuron (Gonzalex et al. 1995). A second view involves the H^+ – generated inhibition of background (TASK1/3) K^+ currents in the glomus cells. The resulting depolarization activates voltage-gated Ca^{++} channels. The entering Ca^{++} attaches to neurotransmitter-containing vesicles which dock on the inner surface of the glomus cell and exocytose their contents across the synapse to appropriate receptors on the abutting afferent neuron (Buckler 2015; Zhang and Nurse 2004).

1.4 O_2 – Detecting Elements in the Respiratory System

1.4.1 Detection in the CNS

Oxygen is sensed by several types of cells in the CNS. But it is not at all clear this influences homeostatic control via respiration. The detection of low oxygen by specialized receptors in the CNS to increase respiration does not seem to have significant data in support of that possibility, though hypoxia does affect cells in the CNS, as it does systemically. Some cells are excited; others, depressed. Again paradoxically, some depressed cells may cause excitation in some other part of the respiratory cell linkage chain. But generally hypoxia produces CNS neuronal depression (Bisgard and Neubauer 1995).

1.4.2 Detection by the Carotid Body

The principal detector of oxygen in vertebrates is the carotid body (CB) found bilaterally at the bifurcation of the common carotid artery into its internal and external branches (Fidone and Gonzalez 1986). The first known report of the carotid body (CB) structure appeared in the January 31, 1743 dissertation defense by Hartwig William Louis Taube in the lab of the great German physiologist, Albrecht von Haller. Occasional works in the CB area appeared in the nineteenth century; many focused on cardiorespiratory reflex responses. In 1900 Pagano (1900) and Siciliano (1900) also located the origin of

reflex effects in the periphery. Heinrich Hering (1866–1948) in papers from 1923 to 1927 (Hering 1923) further established the role of the peripheral nerves in the reflex effects. So biological detection remained in the area of reflex effects. In the mid- to late 1920's two great centers pursued a deeper appreciation of the morphology and intercellular relations of the CB (Fig. 1.5) in the person of Fernando De Castro working in Madrid (DeCastro 1926, 1928). The second group of Corneille and J.F. Heymans and colleagues pursued the mechanisms of the cardiopulmonary reflexes by stimulating the carotid and aortic locations (Heymans J-F and Heymans C 1927; Heymans C et al. 1930). The story surrounding their interactions with each other and their colleagues has been told frequently in the past. Their work went on well into the 1930s and for which Corneille Heymans won the 1938 Nobel Prize in Physiology or Medecine. De Castro was such a strong influence on Heymans that many thought he should have shared the Prize. This thought does have credibility since it is clear from the reports of each that De Castro had correctly assigned the role of the CB before C. Heymans had done so. Each contributed to a deepening of our understanding of the CB's next door neighbor, the carotid sinus, principal detector and regulator of arterial blood pressure.

Later years has revealed several other reflex effects resulting from CB stimulation in addition to the control of O_2 and CO_2 homeostasis (Fitzgerald and Lahiri 1986). Recent studies have focused on the cellular and molecular mechanisms involved in the *detection* of hypoxia, hypercapnia, and acidosis (Fidone and Gonzalez 1986). Histological studies had confirmed that the carotid body's glomus cells were filled with neurotransmitter- containing vesicles.

Many studies confirmed the presence of ACh, ATP, DA, NE, 5HT, GABA, neurokinin A. Appropriate receptors were also located: Cholinergic muscarinic (M1, M2), ncotinic, dopamine (D2), GABA B, and purinergic (P2X2Y and others (Fig. 1.6)). Recent reports have uncovered what might be called modulators of carotid body neural output: NO, H_2S, adenosine. And other recent reports have identified TRPV1 channels and the olfactory receptor, Olf78, (Chang et al. 2015) as having roles in chemodetection. One commonly accepted cascade of events in detection of lowered levels of oxygen has been: hypoxia reduces K^+ traffic in channels including TASK K^+ channels (Buckler 2015;

Fig. 1.5 Composite of several of De Casto's drawings showing the neurotransmitter-containing Type I cells with afferent neurons applied to them. Note the different type of endings…calyx, rete, simple fiber (with permission Oxford University Press/ American Physiological Society)

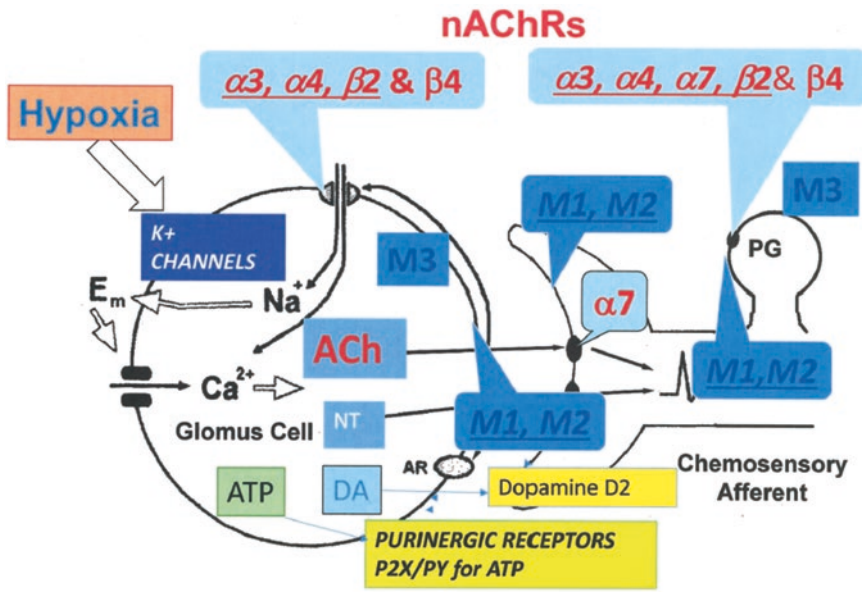

Fig. 1.6 Neurotransmitter receptors in the cat carotid body. A composite of studies, mostly provided by Shirahata, showing the location of various types of cholinergic receptors and highlighting the sub-units of the nicotinic receptors. These operate in the biological detection of O_2 by the carotid body (Shirahata et al. 1998; Hirasawa et al. 2003)

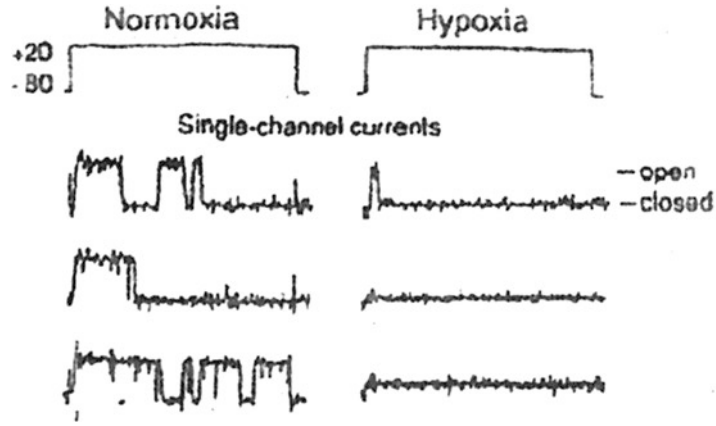

Fig. 1.7 K^+ channel behavior during hypoxia**.** Hypoxia inhibits current through this K^+ channel in the membrane of the Type I cell. In so doing the cell becomes depolarized which opens voltage-gated Ca^{2+} channels. Ca^{2+} rushes in, adhering to the transmitter-containing vesicles which exocytose their contents into the cleft between the cell and abutting afferent neuron. (Adapted from Lopez-Barneo 1994; with permission Rightslink/Elsevier)

Lopez-Barneo 1994), Fig. 1.7 elevating resting membrane potential; this depolarizing action opens voltage-gated calcium channels; the entering Ca^{++} binds to the vesicles; a protein, synaptophysin or physophilin docks the vesicles on the inner surface of glomus cells, and they exocytose their contents into a synaptic-like cleft between the glomus cell and the abutting afferent neuron. But in some species there is substantial evidence that H_2S, known to increase in an hypoxic environment, is thought to be the excitatory agent closing the maxi K^+_{BK} channel (Peng et al. 2010). However, other proposed mechanisms of hypoxic chemotranduction (e.g., "metabolic hypotheses") have suggested that O_2 sensing by chemoreceptor cells is linked to

mitochondrial structure and function (Buckler 2015). ATP is central to this explanation. As chemoreceptor neural output increases with the decreasing O_2, genesis of ATP must confront lowered O_2. A further problem is the link between a decrease in ATP and the Ca^{++}-triggered release of neurotransmitters has remained unclear. Finally, there are several recent reports of genetic differences in the detection of hypoxia as well as in carotid body structure and function (Weil 2003; Weil et al. 1998; Balbir et al. 2007, 2006; Yamaguchi et al. 2006). The above treatment is really focused on *acute* exposure to lowered PaO_2.

The ventilatory response to long term exposure to hypoxia has some phases, and the story is not yet clear. There is the hypoxic ventilatory run-off or depression which occurs 10–15 min after the CB-mediated increase in ventilation. But then there is the acclimatization to both short term and long term exposure to hypoxia. CNS neurons are in general turned off by hypoxia and therefore not responsible for the increased ventilation of acclimatization. This phenomenon does seem to have its locus in the CB, perhaps in a reduced sensitivity of the D2 dopamine receptor on the CB's afferent neuron to the NTS. The complexity surrounding this situation is fully reviewed recently (Bisgard and Neubauer 1995). Both areas of ventilatory changes need further study. A final point of "integrative control" which must be included is the finding by Philipson (Phillipson et al. 1981), and others that for rhythmic breathing generated in the CNS there is an absolute need for input from peripheral receptors. One study (Sullvan et al. 1978) in healthy unanesthetized dogs combined metabolic alkalosis with slow wave sleep, vagal blockade, and hyperoxia. Respiratory frequency was reduced to one breath/minute. Such data clearly demonstrate that afferent respiratory stimuli from the periphery are essential for sustaining adequate ventilation.

1.5 Summary

After a brief look at where this planet's O_2 and CO_2 originated inorganically and organically, the method of detecting the two gases biologically so that their homeostatic control would benefit the organism was found to be breathing. Early investigators of the lung, heart, and breathing were quite confused, and many thought the lung and heart were involved in the cooling of the inner body. Major advances in the understanding of the lung, heart, and breathing came with the seventeenth century Oxford group. They made it perfectly clear that air passing into the lungs was necessary for life; and this air did something beneficial to the blood. A next step identified CO_2 as a stimulus to breathing; not quite clear yet was the impact of hypoxia *per se*. Finally determined was the discovery that it was the $[H^+]$ in the CSF generated by CO_2 that was detected by structures in the medulla. Peripheral detection of hypoxia was by the CB, which also senses CO_2. More advanced studies of the CB have uncovered subcellular and even genetic modification of this detection. Finally, though it was clear that CO_2 seems to be the major stimulus to respiration acting centrally and peripherally, work has shown that the rhythmic breathing in the homeostatic condition is produced by CNS elements in the pons and medulla. But they must have input from peripheral receptors.

References

Balbir A, Okumura M, Schofield B, Coram J, Tankersley CG, Fitzgerald RS, O'Donnell CP, Shirahata M (2006) Genetic regulation of chemoreceptor development in DBA/2J and A/J strains of mice. Adv Exp Biol Med 580:99–104

Balbir A, Lee H, Okumura M, Biswal S, Fitzgerald RS, Shirahata M (2007) A search for genes that may confer divergent morphology and function in the carotid body between two strains of mice. Am J PhysiolLung Cell Mol Physiol 292:L704–L715

Bisgard GE, Neubauer JA (1995) Peripheral and central effects of hypoxia. In: Dempsey JA, Pack AI (eds) Regulation of breathing, 2nd edn, Revised and Expanded. Marcel Dekker Inc, New York, pp 617–668

Buckler KJ (2015) TASK channels in arterial chemoreceptors and their role in oxygen and acid sensing. Pflugers Arch – Eur J Physiol 467:1013–1025

Chang AJ, Ortega FE, Riegler J, Madison DV, Krasnow MA (2015) Oxygen regulation of breathing through an olfactory receptor activated by lactate. Nature 527:240–244

De Castro F (1926) Sur la structure et l'innervation de la glande intercarotidienne (Glomus caroticum) de l'homme et des mammiferes, et sur un noveau system d'innervation autonome du nerf glossopharyngien. Trav Lab Rech Biol Univ Madrid 24:365–432

De Castro F (1928) Sur la structure et l'innervation du sinus carotidien de l'homme et des mammiferes. Noveaux faits sur l'innervation et la fonction du glomus caroticum. Trav Lab Rech Biol Univ Madrid 25:331–380

Dempsey J, Forster H (1982) Mediation of ventilatory adaptations. Physiol Rev 62:262–346

Fidone SJ, Gonzalez C (1986) Initiation and control of chemoreceptor activity in the carotid body. In: Handbook of physiology section 3: The respiratory system volume II control of breathing. American Physiological Society, Bethesda, pp 247–312

Fitzgerald RS, Lahiri S (1986) Reflex responses to chemoreceptor stimulation. In: Handbook of physiology section 3: the respiratory system volume II control of breathing. American Physiological Society, Bethesda, pp 313–362

Fredericq L (1890) Sur la circulation cephalique croisse, ou echange de sang carotidien entre deux animaux. Arch Biol 10:127–130

Gonzalex C, Dinger B, Fidone S (1995) Mechanisms of carotid body chemoreception. In: Dempsey JA, Pack AI (eds) Regulation of Breathing, 2nd edn, Revised and Expanded. Marcel Dekker Inc, New York, pp 391–471

Haldane JS, Priestley JG (1905) The regulation of lung-ventilation. J Physiol Lond 32:225–255

Hering HE (1923) Der Karotisdruckversuch. Münch Med Wschr 42:1267–1290

Heymans J-F, Heymans C (1927) Sur les modificationes directes et sur la regulation reflexe de l'activite du centre respiratoire de la tete isolee du chien. Arch Int Pharmacodyn Ther 33:273–372

Heymans C, Bouckaert J-J, Dautrebande L (1930) Role reflexogene respiratoire des zones vaso-sensibles cardio-aortique et sino-carotidiennes. Ion Hydrogene,CO_2 sinus carotidiens et reflexes respiratoires. C R Soc Biol 105:881–884

Hirasawa S, Mendoza JA, Jacoby DB, Kobayashi C, Fitzgerald RS, Schofield B, Chandrasagaran S, Shirahata M (2003) Diverse cholinergic receptors in the cat carotid body unit. Adv Exp Med Biol 536:313–319

Jacobs MH (1920) The production of intracellular acidity by neutral and alkaline solutions containing carbon dioxide. Am J Phys 53:457–463

Kolobow T, Gattinoni L, Tomlinson TA, Pierce JE (1977) Control of breathing using an extracorporeal membrane lung. Anesthesiol 46:138–141

Kussmaul A, Tenner A (1857) Untersuchungen uber Ursprung und Wesen der fallsuchtartigen Zuckungen bei Verblutung sowie der Fallsucht uberhaupt. Utersuchungen zur Naturlehre Menschen Thiere 3:1–124

Lane N (2003) OXYGEN, the molecule that made the world. Oxford University Press Inc., New York

Leusen I (1954) Chemosensitivity of the respiratory center. Influence of CO_2 in the cerebral ventricles on respiration. Am J Phys 176:39–44

Loeschcke H, Koepchen H, Gertz K (1953) Uber den Einfluss von Wasserstoffionenkonzentration und CO_2-druck im Liquor cerebrospinalis auf die Atmung. Pfluger's Arch Gesamte Physiol 266:628–641

Lopez-Barneo J (1994) Oxygen-sensitive channels: how ubiquitous are they? Trends Neurosci 17:133–135

Meischer-Rusch F (1885) Bemerkungen zur Lehre von den Atmbewegungen. Arch Anat u Physiol, Leipzig 6:355–380

Mitchell R, Loeschcke H, Massion W, Severinghaus J (1963) Respiratory responses mediated through superficial chemosensitive areas on the medulla. J Appl Physiol 18:523–533

Nattie EE (1995) Central chemoreception. In: Dempsey JA, Pack AI (eds) Regulation of breathing. Marcel Dekker, New York, pp 473–510

Nattie EE, Li A (2006) Central chemoreception 2005: a brief review. Autonom Neurosc: Basic & Clin 126–127:332–338

Pagano G (1900) Sur la sensibilite du coeur et des vaisseaux sanguins. Arch Ital Biol 33:1–36

Pappenheimer J, Fencl V, Heisey S, Held D (1965) Role of cerebral fluids in control of respiration as studied in unanesthetized goats. Am J Phys 208:436–450

Peng YH, Nanduri J, Raghuraman G, Souvannakitti D, Gadalla MM, Kumar GK, Snyder SH, Prabhakar NR (2010) H_2S mediates O_2 sensing in the carotid body. PNAS 107:10719–10724

Phillipson EA, Duffin J, Cooper JD (1981) Critical dependence of respiratory rhythmicity on metabolic CO_2 load. J Appl Physiol Respirat Environ Exercise Physiol 50:45–54

Shirahata M, Ishizawa Y, Rudisill M, Schofield B, Fitzgerald RS (1998) Presence of nicotinic acetylcholine receptors in cat carotid body afferent system. Brain Res 814:213–217

Siciliano L (1900) Les effets de la compresssion des carotides sur la pression, sur le coeur et sur la respiration. Arch Ital Biol 33:338–344

Sullivan CE, Kozar LF, Murphy E, Phillipson EA (1978) Primary role of respiratory afferents in sustaining breathing rhythm. J Appl Physiol 45:11–17

Weil JV (2003) Variation in human ventilatory control – genetic influence on the hypoxic ventilatory response. Respir Physiol Neurobiol 135:239–246

Weil JV, Stevens T, Pickett CK, Tatsumi K, Dickinson MG, Jacoby CR, Robinson DM (1998) Strain-associated differences in hypoxic chemosensitivity of the carotid body in rats. Am J Physiol Lung Cell Mol Physiol 274:L767–L774

Winterstein H (1911) Die Regulierun der Atmung durch das Blut. Pfluger's Arch Gesamte Physiol 138:167–184

Winterstein H (1921) Die Reaktionstheorie der Atmungsregulation. Pfluger's Arch Gesamte Physiol 187:293–298

Yamaguchi S, Balbir A, Schofield B, Coram J, Tankersley CG, Fitzgerald RS, O'Donnell CP, Shirahata M (2006) Genetic influence on carotid body structure in DBA/2J and A/J strains of mice. Adv Exp Med Biol 580:105–109

Zhang M, Nurse CA (2004) CO_2/pH chemosensory signaling in co-cultures of rat carotid body receptors and petrosal neurons: role of ATP and ACh. J Neurophysiol 92:3433–3445