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Olfactory Marker Protein in the Human Carotid Body

Andrea Mazzatenta[1], Susi Zara[2], Sara Invitto[3], Andrea Porzionato[4], Amelia Cataldi[2], Camillo Di Giulio[1], Mieczyslaw Pokorski[5,*]

[1]Neuroscience, Imaging and Clinical Science Department, "G. d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy
[2]Department of Drug Sciences, "G. d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy
[3]Department of Biological and Environmental Sciences and Technologies, University of Salento, 73100 Lecce, Italy
[4]Department of Human Anatomy and Physiology, University of Padova, 35121 Padova, Italy
[5]Institute of Health Sciences, Opole University, 45-060 Opole, Poland
*Correspondence: m_pokorski@hotmail.com (Mieczyslaw Pokorski)
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Background: Transduction mechanisms of the hypoxic chemoreflex elicited by carotid body (CB) chemoreceptor cells remain unclear. Recent studies direct attention to the plausible link between CB and olfactory chemoreceptor functions.
Methods: Here we used immunohistochemistry to investigate the distribution and localization of olfactory marker protein (OMP) in human CB. Carotid bodies were collected post-mortem from hospital patients aged 27–76 years who died from reasons unrelated to chronic pulmonary or cardiovascular disorders. We used specific antibodies to selectively identify CB cells and OMP in tissue sections. The binding of antibodies to target antigens was visualized with the Ultra Vision detection system.
Results: We show that OMP is abundantly present in the cytoplasm of CB chemoreceptor cells. The presence of OMP in these cells indicates that the olfactory system may participate in shaping the chemosensory CB function.
Conclusions: The findings support the notion that the transduction mechanisms of chemoreceptive systems contain a degree of homology, irrespective of the anatomical localization and the functional role these systems fulfill. The ectopic presence of OMP in CB broadens the current understanding of the mechanisms underlying chemosensory responses.

Keywords: carotid body; chemoreceptor cells; olfaction; olfactory marker protein; oxygen sensing

Introduction

The evolution of the chemoreceptive ability in mammals reflects the homeostatic adaptation to meet metabolic requirements for changing environmental challenges. Chemosensing is uniquely specialized depending on the target being sensed, leading to the development of biological measures to probe a fine-tuned milieu [1]. The carotid body (CB) is an 'internal' chemosensing organ whose natural stimuli are hypoxia, hypercapnia, and acidic shift in the arterial blood. However, the organ's main role is to induce hyperventilation in response to blood hypoxia [2–4]. General knowledge is that hypoxia causes the closure of K^+ outward channels in the plasma membrane of chemoreceptor cells followed by Ca^{2+} influx, and the release of neurotransmitters followed by an enhanced neural discharge in the afferent fibers of the carotid sinus nerve which, via the glosso-pharyngeal nerve, is relayed to the brainstem respiratory network [5,6]. Molecular transduction pathways of oxygen sensing in CB are not completely understood and they seem to have been disparate in response to hypoxia, hypercapnia, and acidity [7,8].

The main function of the olfactory system is to detect odors, which is a part of chemosensing. The system consists of sensory neurons of the olfactory epithelium. The neurons, which relay signals to cortical areas, express receptors that extend out into the airspace to sense odorants [9,10]. Olfactory sensory neurons use well-conserved transduction pathways consisting of G-protein, adenylyl cyclase III, and olfactory marker protein (OMP) [11]. Olfactory receptors are expressed ectopically in a variety of non-olfactory and non-chemosensing tissues, having the likened composition of messenger proteins involved with the monitoring of extracellular chemical cues [12,13]. OMP is expressed in olfactory neurons and is a powerful marker to investigate the physiology of olfaction rather than a single olfactory receptor [14].

The hyperventilatory response to hypoxia is the most characteristic trait of CB function. Recently, the olfactory receptor 78 (Olfr78) has been identified in CB and its global deletion inhibits the ventilatory response to mild but not severe hypoxia [15,16]. Earlier studies reported transcripts for olfactory receptors and OMP in mouse CB [17,18]. In those studies, RNA sequencing and whole-genome microarrays were performed to compare gene expression in CB and the adrenal medulla. The adrenal cells share functional and morphologic similarities with CB chemoreceptors but do not respond to hypoxia. The Olfr78 receptor

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was expressed in CB but not in the adrenal medulla. Further, galanin, a neuropeptide that contributes to the development of olfactory neurons and neuronal plasticity [19] is expressed in CB chemoreceptors [20,21]. These findings suggest a functional link between CB and olfactory chemoreceptive systems.

An understanding of the functional role of OMP in CB is veiled by a multifarious and often unclear role of ectopic OMP presence in a variety of tissues, on the one side [12,22], and the species differences in the composition of molecules essential for chemosensory responses, on the other side. The latter is pointedly exemplified by noradrenaline whose content is substantially higher than that of dopamine in cat and guinea pig CBs, although dopamine is the predominant amine in the rabbit and ferrets [23]. Likewise, dopamine is an excitatory transmitter in rabbit CB while it plays just a modulatory role in cat CB [24].

The ectopic presence of OMP has been confirmed in rodent CB only, with no clue for the physiological role. We reasoned that the role of OMP in CB could be better systematized into one coherent body of knowledge if this protein were present in far-flung mammalian species. Here we investigated the presence of OMP in human CB. Since the organ is yet unavailable for direct studies in humans due to its minute size and localization at the bifurcation of the common carotid artery, we used post-mortem CB tissue excised from cadavers. We report the abundant presence of OMP in human CB.

Materials and Methods

Human carotid bodies were harvested from cadaver donors enrolled in the Body Donation Program of the Section of Human Anatomy of the University of Padova [25] in compliance with European, Italian, and regional guidelines [26]. The Body Donation Program is recognized as the Center of the Veneto Region for Body Donation (Decree no. 245 of 8 March 2019) and is on the list of the centers authorized by the Italian Ministry of Health (Decree of 23 August 2021) to harvest post-mortem tissue specimens. All donors accepted the use of their corpses for research purposes. The post-mortem tissue images presented herein could in no way be linked to individual donors. Therefore, additional ethical and consent-seeking requirements were waived by the institutional research review committee.

Collection of Carotid Bodies

Carotid bodies (n = 12) were collected post-mortem from hospital patients aged 27–76 years who died from reasons other than any chronic pulmonary or cardiovascular conditions. Exclusion criteria at the autopsy examination included cardiac hypertrophy, myocardial infarction, and signs of CB tissue degeneration revealed during standard histological staining. Additionally, the possible influence of the death-to-autopsy interval was examined statistically as previously described [27].

Immunohistochemistry

CB specimens were fixed in 10% formalin, embedded in paraffin wax, serially cut in 3-μm slices, stained with a Mallory trichrome, and examined under light microscopy. Immunohistochemistry was performed using antibodies and commercial kits, according to the manufacturers' recommendations. Briefly, the identification of chemoreceptor Type I cells was performed using an H-11 mouse anti-galanin monoclonal antibody (H-11) (sc-166431), dilution 1:100, and a mouse anti-nestin monoclonal antibody (10c2) (sc-23927), dilution 1:100 (both from Santa Cruz Biotechnology; Santa Cruz, CA, USA). Sustentacular cells, the glial-like type II cells in CB, were identified using anti-glial fibrillary acidic protein (GFAP) mouse monoclonal antibody (orb18222), dilution 1:200 (Biorbyt, Cambridge, UK). The identification of OMP in chemoreceptor cells was performed using rabbit polyclonal anti-OMP antibody (orb312414), dilution 1:100 (Biorbyt; Cambridge, UK). The developing kits consisted of HRP (Horseradish Peroxidase; LPH170223) Polymer & DAB (3,3′-Diaminobenzidine; HSX160719AF) Plus Chromogen and Lab Vision UltraVision LP (Labeled Polymer) Value Detection System (Thermo Fisher Scientific, Waltham, MA, USA).

Data Acquisition and Analysis

Light microscopy and data acquisition were performed using a Leica DM 4000 (Double Monocular) microscope (serial no. 15816) equipped with a DFC 320 (Digital Firewire Color) camera digital acquisition system and Leica QWin Plus version 3.5 software (executable file: pcmc32.exe) to compute areas showing immunoreactive materials (Leica Cambridge; Cambridge, UK). One-way ANOVA (Analysis of Variance) was used to assess differences in immunoreactive materials, with the α-level set at 0.001. The analysis was performed using commercial statistical packages of IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, NY, USA) and OriginPro version 2017 (OriginLab Corp., Northampton, MA, USA).

Results

Carotid Body Morphology

The morphological structure of human CB parenchyma is depicted in Fig. 1. The organ consists of discrete clusters of chemoreceptor cells with sustentacular cells at the outer edge, penetrated by a net of capillaries. The clusters are separated from each other by connective septa.

Immunostaining of Olfactory Marker Protein

Fig. 2 shows the OMP immunoreactive material (left column) compared to a negative control where the anti-

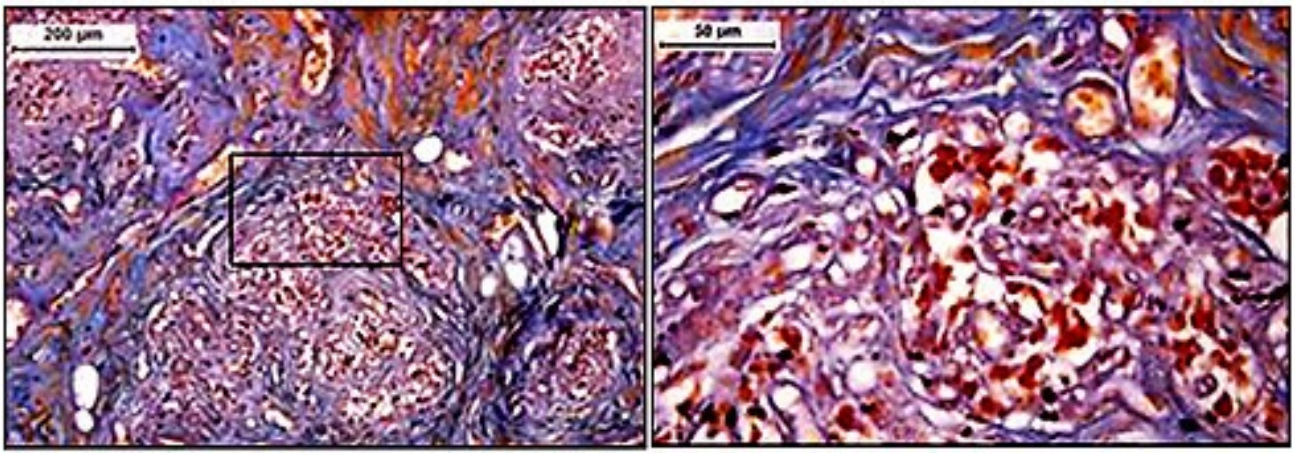

Fig. 1. Clusters of carotid body chemoreceptor cells with sustentacular cells at the outer edge, penetrated by capillaries. The framed central part of the photomicrograph is blown up in the right panel (Mallory trichrome stain).

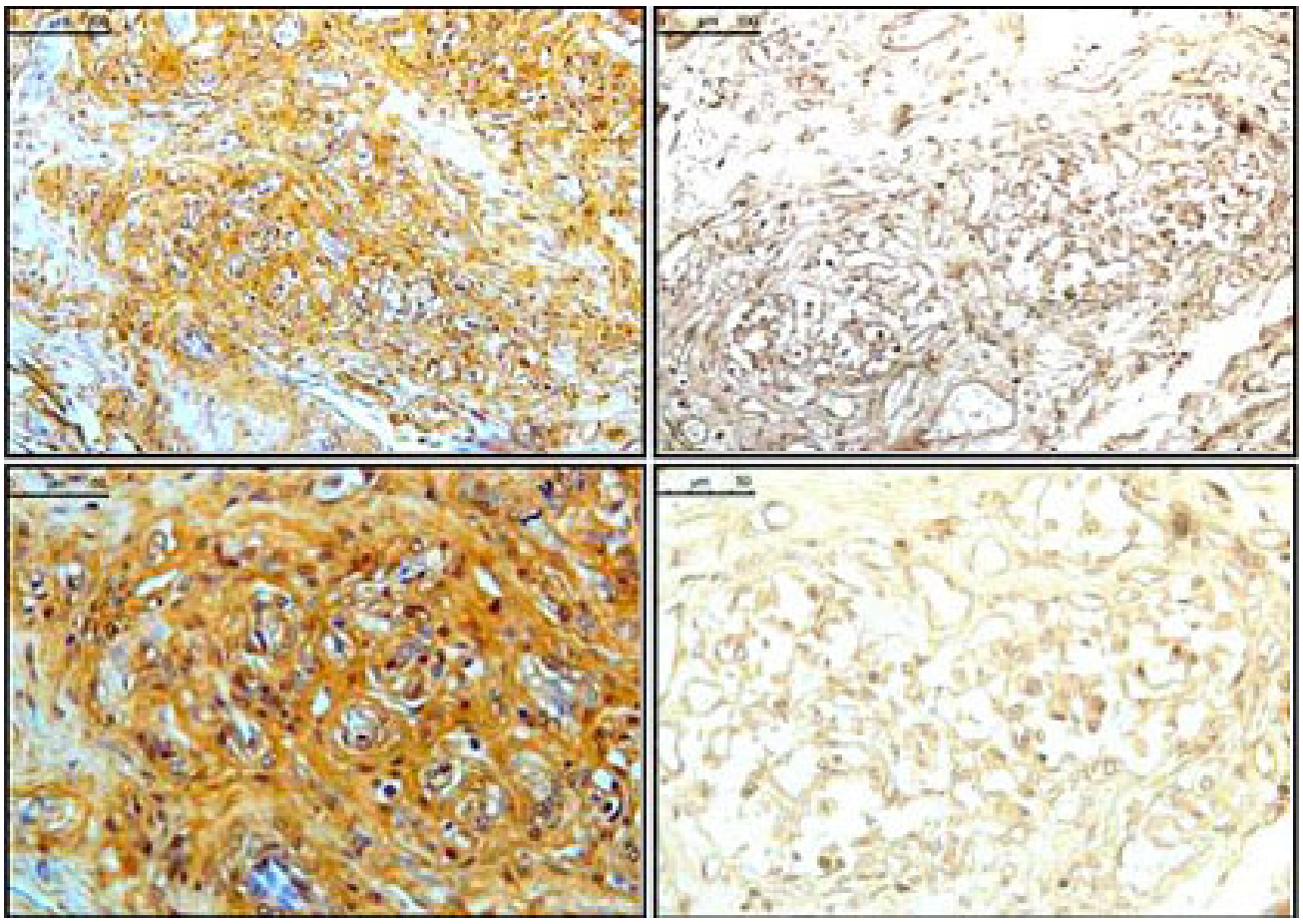

Fig. 2. Clusters of carotid body chemoreceptor cells showing immunoreactivities against anti-olfactory marker protein (OMP) antibodies (left panels) as compared to negative controls where the anti-OMP antibodies were omitted (right panels). Scale bars are 100 μm in the upper panels and 50 μm in the bottom panels.

OMP antibodies were omitted (right column). High intensity of immunoreactive material corresponding to the anti-OMP antibody binding signal was explicitly seen in chemoreceptor cells.

OMP-like immunoreactive material in CB parenchyma was represented as black-and-white images and analyzed as 3D (three-dimensional) matrices to quantify the percentage of the immunostained area using the anti-OMP antibodies versus the negative control where

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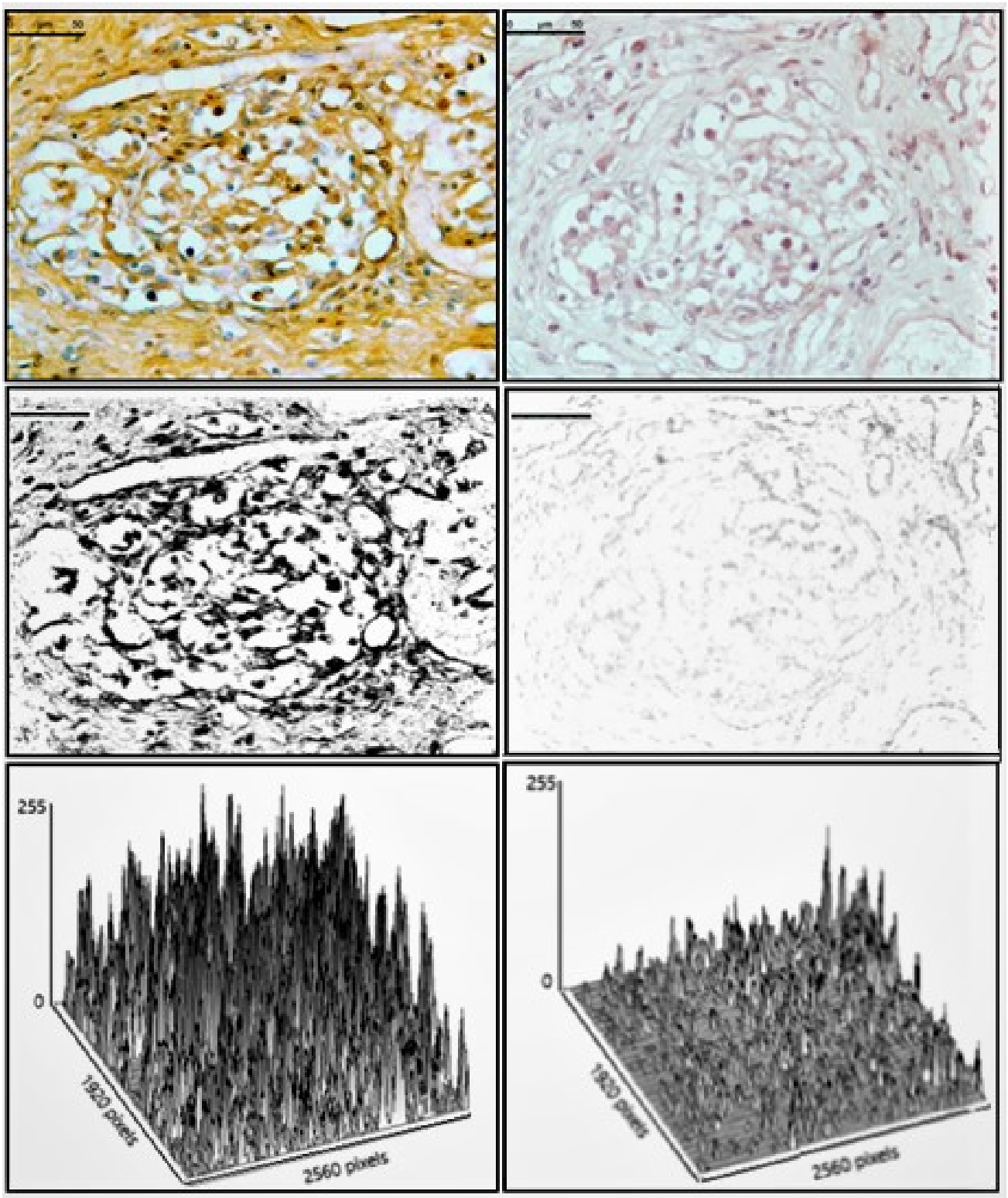

Fig. 3. A cluster of CB carotid body chemoreceptor cells expressing immunoreactivities against olfactory marker protein (OMP) antibodies (left panels) as compared to negative controls where the anti-OMP antibodies were omitted (right panels). The top row shows immunoreactive material and its lack in the control. Black-and-white images in the middle row show the signals used for the area calculation of immunoreactive material intensity evoked by peroxidase reactions in both specimens. Scale bars in the four upper morphological photomicrographs are 50 μm. The 3D images in the bottom row compare the percentage of immunoreactive area in positive and negative specimens.

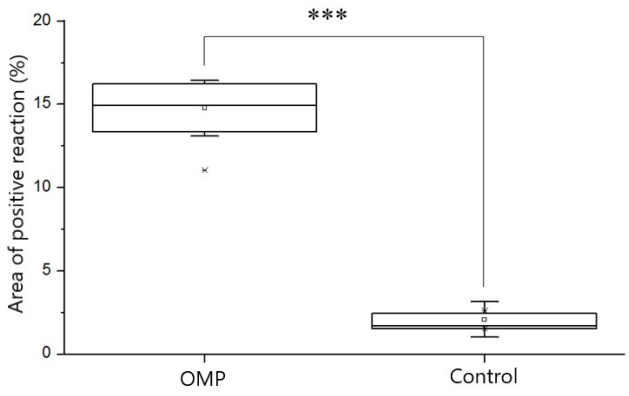

Fig. 4. Box (SD) and whiskers (SE) chart comparing the percentage of the positive immunoreactive area against the anti-olfactory marker protein (OMP) antibody to negative control in CB. $^{***}p < 0.001$.

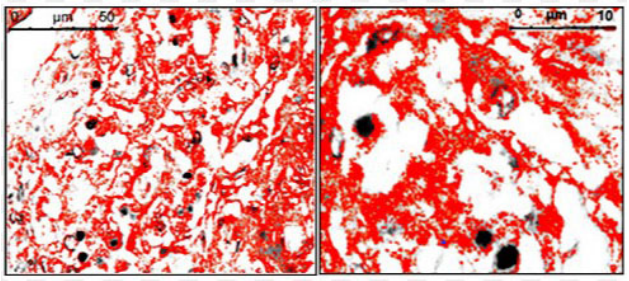

Fig. 5. Olfactory marker protein (OMP)-like immunoreactivity. The sham red color was superimposed on the black-and-white three-dimensional images. The dark grey randomly scattered round elements are chemoreceptor cells' nuclei. The red shade highlights the cytoplasmic localization of OMP in chemoreceptor cells.

the antibodies were omitted (Fig. 3). There were significant differences between the mean area of the anti-OMP antibody and the control (14.8 ± 2.9% vs. 2.1 ± 0.8%, respectively, $p < 0.001$; One-way ANOVA). These results are graphically illustrated in Fig. 4.

Localization of Olfactory Marker Protein in Carotid Chemoreceptor Cells

To visualize the OMP localization, the black and white images were superimposed using sham red coloring to highlight the areas of positive immunoreaction against OMP. This technique revealed the cytoplasmic distribution of OMP in chemoreceptor cells (Fig. 5).

Discussion

Here we found the presence of OMP, a key olfactory protein that regulates receptor-mediated function in non-olfactory tissues, in the human CB. OMP immunostaining was identified in the cytoplasm of chemoreceptor cells. The finding fits well into the recently reported presence of Olfr78 in carotid body tissue in mice [15,16]. Those studies pointed to the possible functional role of Olfr78 since the acute hypoxic ventilatory response and cardiorespiratory adaptation, characteristic of CB function, were impaired in global Olfr78 null mice. The G protein-coupled Olfr78 was identified in chemoreceptor cells isolated from mice in the immunohistochemical analysis following a transcriptome *in-situ* hybridization [18]. Olfactory receptors in CB had also been reported in earlier studies [17,28].

In this study, we focussed on OMP as a target olfactory protein rather than any specific olfactory receptor to infer the olfactory-mediated role in CB chemosensing. This approach is widely used in the literature [12,29]. Since OMP is a unique protein in that it is present in both vertebrate and invertebrate species [30], it is assumed to have a key functional role in the olfactory transduction pathway and signal amplification [31]. OMP, along with odorant receptors, is also expressed in different chemosensory tissues [12,32]. Further, the OMP gene is conserved in rodent and human genomes [14,33]. Thus, this protein well connects the chemosensory functions of two distant species discussed in this study.

The presence of OMP in chemoreceptor cells should be considered ectopy as there is no definable role of CB in olfactory function reported yet. This presence underscores, however, a great deal of conserved homology in the composition of messengers involved with the monitoring of anatomically and functionally disparate chemosensory systems, having a common role of sensing chemical cues. Ectopic olfactory receptors are engaged in chemosensory modulation, hormone, and neurotransmitter secretion, and cell migration in different mammalian tissues [13,32]. The cytoplasmic localization of OMP in chemoreceptor cells found in the present study is in line with the distribution of a myriad of neurotransmitters, receptors, ion channels, and neuroactive modulators known to be involved in CB chemosensing [6–8].

The issue that limits the current understanding of the role of the olfactory system in CB is that no distinct function could be firmly ascribed to it. Chang *et al.* [17] have suggested that Olfr78 might sense hypoxia through the concurrent changes in lactate, a metabolite that is produced when oxygen declines, with the consequent induction of Ca^{2+} transients and stimulation of chemoreceptor cell discharge. However, Peng *et al.* [16], based on the global deletion of Olfr78, have shown that lactate or other common ligands of Olfr78 are not essential for hypoxia sensing, the most genuine CB chemoreflex. Thus, implicitly a modulatory rather than an executive function of olfactory receptors is ascribed to chemosensing.

The uncertainty surrounding the role of the olfactory system's elements in CB may stem from the investigations performed exclusively on mice whereas this system is expressed across various species, organs, and tissues [34,35].

Hypoxic chemoreflex is a functional landmark in all mammals. The present finding of OMP in CB of humans, a species most distant from rodents, strongly supports the biological plausibility of a link between the olfactory system in the organ's chemosensing.

Conclusions

We conclude that the ectopic presence of an olfactory marker protein in chemoreceptors of human CB, along with the known substantial stimulus transduction homology in chemoreceptive systems, suggests the olfactory system be at play in shaping hypoxic chemosensing. The kind and degree of specific engagement of olfactory proteins in CB chemosensing require further explorations using alternative study designs evaluating changes in transcriptional olfactory pathways during hypoxia or the use of animals with specific olfactory gene knockouts.

Author Contributions

AM—designed and performed the research, and analyzed the data; SZ and SI—provided help and advice during the study; AP—provided help in harvesting tissue from cadavers and performing immunohistochemistry and its analysis; AC and CDG—provided help and advice during the experiments; MP—reassessed, reanalyzed the data, arranged the artwork, and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Procedures performed in this study were in accord with the 1964 Helsinki Declaration and its later amendments, national legislation, and institutional requirements.

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Conflict of Interest

Mieczyslaw Pokorski is an editorial board member of the JBRHA. The other authors declare no conflict of interest.

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