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Luschka and the carotid body

Luschka e o corpo carotídeo

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ABSTRACT

The 'carotid body' is a small structure sited at the bifurcation of the common carotid artery. The macroscopic features of the carotid body, and items of the extrinsic nervous, and vascular supplies, were initially described by Taube (1743), complemented by a number of authors that followed, proceeding until Luschka (1962), who added the first microscopic study. The macroscopic features of the carotid body, including location, extrinsic innervation, and vascular supply, then provided, were described in a relatively satisfactory manner. However, despite Luschka's great and admirable effort, the microscopic findings seem to be flawed, what can be ascribed to the technical limitations at the time, and the artifacts due to the used procedures. Nevertheless, there is no doubt that Luschka and his forerunners provided an important step for forthcoming research on the carotid body, and its innervation.

Keywords: carotid body, type I cells, type II cells, carotid sinus nerve

RESUMO

O 'corpo carotídeo' é uma pequena estrutura situada na bifurcação da artéria carótida comum. Os aspectos macroscópicos do corpo carotídeo e itens sobre o suprimento nervoso e vascular extrínsecos foram descritos inicialmente por Taube (1743), complementados por um certo número de autores que seguiram, prosseguindo até Luschka (1962), que acrescentou o primeiro estudo microscópico. Os aspectos macroscópicos do corpo carotídeo, incluindo localização, inervação extrínseca e suprimento vascular, então providos, foram descritos de modo relativamente satisfatório. Entretanto, apesar do grande e admirável esforço de Luschka, os achados microscópicos aparecem falhos, o que pode ser atribuído às limitações técnicas daquele tempo e a artefatos devidos aos procedimentos utilizados. Todavia, não há dúvida que Luschka e seus precursores proveram um importante passo para pesquisas que vieram sobre o corpo carotídeo e da sua inervação.

Palavras-chave: corpo carotídeo, células tipo I, células tipo II, nervo do seio carotídeo

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INTRODUCTION

The 'carotid body' (or *glomus caroticum*) is a very small round or ovoid structure embedded in the adventitia in the angle of the bifurcation of the common carotid artery. The gland is formed by groups of cells supported by a delicate network, forming numerous round lobules of varied sizes, consisting of round or oval clusters of glomus cells, each enclosed by a thin collagenous capsule, and the whole surrounded by a thin fibrous capsule. The histological structure of each cluster comprises two kinds of cells, the glomus type I cells ('chief cells' or 'principal cells'), most numerous, and glomus type II cells ('sustentacular cells') (neuroglial cells). The type I cells possess an abundant light and eosinophilic cytoplasm, containing vesicles, and a large oval or rounded nucleus, comprising three subtypes - light, dark and progenitor. Their cytoplasmic vesicles are rich of biogenic amines and peptides, related to the production of neurotransmitters, including acetylcholine, catecholamines (mostly DA, and also 5-HT, NA, and AD) (contained in dense-core vesicles), and neuropeptides (also inside the vesicles), and are seen as true chemoreceptor elements. The type II cells, usually considered as supportive, are fusiform, with elongated nuclei, and envelop clusters of type I cells. Besides, there are ganglionic cells, Schwann cells, fibrocytes, pericytes, mast cells, and eventually others. The 'ganglionic cells' are found isolated or arranged in small clusters, usually situated at the periphery of groups of glomus cells. They are several times larger than chief cells, have an abundant finely granular and basophilic cytoplasm, and large, round, vesicular nuclei. The structure has an abundant nervous supply, coming with the 'carotid sinus nerve', comprising several large bundles of myelinated nerves within the connective tissue surrounding the carotid body or within the septa separating the lobules, and from these, numerous branches extend between the lobules, appearing as many individual fascicles. After entering the lobules, they become unmyelinated, maintaining its relationship to Schwann cells. The small nerves which supply the cell clusters are better seen by silver impregnation, which reveal, at the edges of the clusters, axons forming a plexus, and several axons course into the centre of the cluster, often from one pole. They terminate on chief cells as a variety of nerve endings such as small boutons, discs, menisci, or calyces. The neurotransmitters-neuromodulators released by type I cells act on the afferent endings, which arise from the petrosal ganglion, where they trigger EPSPs in synapsed neurons leading to the respiratory centre. The gland has a rich vascularization, involving a complex network of arteries, capillaries, and veins. The main glomus artery arises mostly from the carotid bifurcation, and enters the proximal pole of the carotid body and gives rise to several, large branches. The latter originate smaller interlobular glomus arteries that supply the lobules, where they resolve into capillary beds, and from there small thin-walled glomus veins run between the lobules to drain into larger veins in the peripheral stroma, which are numerous at the distal pole. The cells have an intimate and complex relationship with the capillary net between each group of cells. [1,2,3,4,5,6,7]

The carotid body receives its innervation from the 'carotid sinus nerve', which originates from the 'glossopharyngeal nerve' soon after its exit from the jugular foramen. It has frequent complex communications with the 'sympathetic trunk' (usually at the level of the superior cervical ganglion), and the 'vagus nerve' (main trunk, pharyngeal branches, and superior laryngeal nerve). It courses on the anterior aspect of the internal carotid artery to reach the 'intercarotid plexus', the 'carotid sinus', and the 'carotid body'. The 'carotid body' contains afferent fibres that have their neurons located in the 'petrosal ganglion' (glossopharyngeal nerve), and centripetal fibres project on to the 'solitary tract nucleus' (caudal part) (IX, X), and chemosensory inputs to the 'commissural' subnucleus.[2,18]

The 'carotid body' is the main peripheral arterial chemoreceptor, and is stimulated by hypoxia, hypercapnia, and pH reduction and its activation produces hyperventilation and stimulates sympathetic output to the vessels (increased blood pressure) and parasympathetic activity to the heart (bradycardia).[2]

HISTORICAL PERSPECTIVE

The discovery of the 'carotid body' may be credited to Hartwig Wilhelm Ludwig Taube (1706-xxxx), who first described the organ and related innervation in his thesis 'On the True Origin of Intercostal Nerves' (*De Vera Nervi Inter Costalis Origine*) (1743), under the presidium of his preceptor Albrecht von Haller. There, he mentions a structure he named 'minuscule ganglion' (*ganglion minutum*) sited at the bifurcation of the [common] 'carotid artery', in the angle between the internal and external carotid arteries, and reports about the long rami that arise from the 'longest intercostal ganglion' (*ganglio hoc longissimo intercostalis*) [superior cervical ganglion], which run behind the [internal?] carotid artery to the angle between the external and internal carotid arteries, where the organ lies, and terminate in the sheath of this artery.[9]

After Taube, Albrecht von Haller (1708-1777), Swiss anatomist, and physiologist, in his 'Elements of the Physiology of the Human Body' (*Elementa Physiologiae Corporis Humani*) (1762), mentioning Taube, cites that from the 'superior cervical ganglion' (*ganglio cervicali superiori*), emerge the 'soft nerves' (*nervi molles*) [sympathetic nerves] [later known as soft Haller's nerves], comprising two or three branches, that accompany the [internal?] carotid artery, the inferior branch being the largest, and forms a plexus at the bifurcation of the carotid artery, where the 'small ganglion' (*ganglion exiguum*), as named by him, is located. He adds that this plexus also receives branches from the trunk of the 'eighth pair' (*octavi paris*) [glossopharyngeal], and from 'laryngeal', and 'pharyngeal' nerves [branches from the vagus], with which they mix.[10,11]

Later, the book of Karl Samuel Andersch (1732-1777), German physician and anatomist, the 'Anatomical-Physiological Treatise on the Nerves of the Human Body II' (*Tractatio Anatomico-Physiologica De Nervis Hvmani Corporis Aliqvibvs II*) (finished in 1751-1755), is published posthumously (1797) by his son Ernst Philipp Andersch. There are described the branches from the 'soft nerves' (*nervorum mollium*) [sympathetic] [Haller's nerves], 'pharyngeal nerve' (*nervo pharyngeo*) [glossopharyngeal], and 'tenth nerve' [vagus] coursing to the carotid angle and to the organ that the author has named 'intercarotid gangliolum' (*gangliolum intercaroticum*), sited at the carotid bifurcation.[11,12]

A long time later, August Franz Joseph Mayer (1787-1865), describes the cervical region (1833), where he mentions the macroscopic aspects of by him named 'intercarotid ganglion' (*ganglion intercaroticum*), lying in the angle of the bifurcation of the common carotid artery, and observing that it is attached to the arterial angle by a 'small ribbon' [a ligamentous strand of tissue (Mayer's ligament), through which artery and innervation pass]. It is connected by one branch or two to the [nervous] plexus formed around the external and internal carotid arteries, which receives descending soft nerves [*nervi molles*] from the superior cervical ganglion. He emphasizes the presence of a fine ramus from the 'lingual pharyngeal cranial nerve' (*Zungenschlundkopfnerven*) [glossopharyngeal nerve], which after giving rami to the net of the soft nerves, spreads in the ganglion. This branch also receives a connecting branch from the vagus nerve.[1,13]

Until the last cited study, the descriptions dealt only with macroscopic issues, as identification, localization, and extrinsic nerves to the region where the organ is located. Next, appeared the first study of its microscopic aspects.

The first detailed study of the 'intercarotid ganglion' (*Ganglion intercaroticum*) in man, macroscopic and microscopic, was provided by Hubert von Luschka (1820 - 1875) (Figure 1), German anatomist, in his book 'The Anatomy of Man in Relation to the Needs of Practical Medicine' (*Die Anatomie des Menschen in Rücksicht auf die Bedürfnisse der praktischen Heilkunde 1.1*), where he provided an anatomical illustration (Plate XXXV) (1862), and in the paper 'On the Gland-like Nature of the so-called Intercarotid Ganglion' (*Ueber die Drusenartige Natur des Sogenannteh Ganglion Intercaroticum*), with an illustration of microscopic aspects (Plate X-B) (1862), where he writes to reveal, according to him, the 'glandular nature' of the structure.[14,15]

Figure 1. Hubert von Luschka [painting by M. Müller-Schüppel (1896)] [05-10-2022] https://commons.wikimedia.org/wiki/File:Hubert_von_Luschka,_Gem%C3%A4lde_von_M._M%C3%BCller-_Sch%C3%BCppel_1896.png

Luschka describes the so named 'intercarotid gland' (*Ganglion intercaroticum*), as he titled it in his article, localizing it in the angle between the common carotid artery bifurcation, the extrinsic innervation, and vascularization, as well as other anatomic characteristics, as size, form, location, colour, texture, as his precursors already have done (Figure 2).[14, 15]

The account of the fine structure begins with his description of the organ, which at first sight appears rather homogeneous, but when compressed between glass plates, and observed under a lens (loupe), it can be seen that the parenchyma of the organ is composed by smaller or larger rounded 'nodules' intermingled in a fibrous tissue.[14,15]

He continues the description focusing on the finer [microscopic] structure, where he observes the organ in a fresh state, without the use of 'reagents' (*Reagens*) [not specified], and next submitted to varied procedures [not

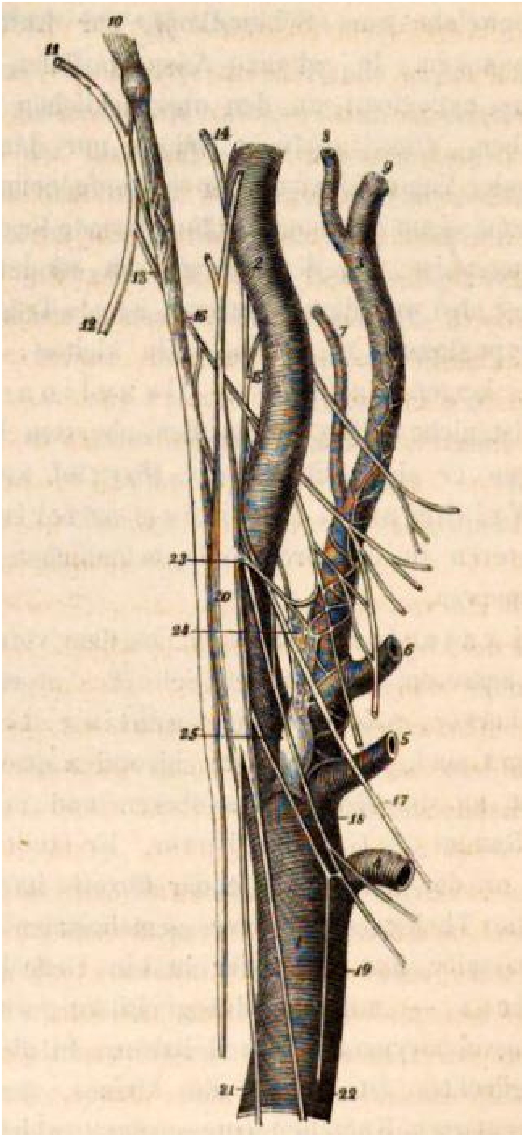

Figure 2. View of the left common carotid artery, bifurcating into the external and internal carotid arteries, and related nerves (Plate XXXV of Luschka's book).[14] **1=common carotid artery**; 2=internal carotid artery; **3=external carotid artery**; 4=superior thyroid artery; 5=lingual artery; 6=external maxillary artery; 7=occipital artery; 8=superficial temporal artery; 9=internal maxillary artery; **10=vagus nerve**; 11=accessory nerve, with 12=external ramus, and 13=internal ramus; **14=glossopharyngeal nerve**, with **15=branches to the 'intercarotid plexus'; 16=pharyngeal nerve of the vagus;17=superior laryngeal nerve**, with **18=external branch arising from the vagus; 19=descending laryngeal branch, joining with a sympathetic fibre; 20=superior cervical ganglion**; **21=sympathetic trunk;** 22=superior cardiac nerve; 23=vasomotor nervous trunk; **24='intercarotid plexus'; 25='intercarotid ganglion'** [carotid body](itens in bold are directly related to the present text)

detailed], applied to dried sections, or specimens hardened in 'chromic acid', and specially preparations of thinly outspread very fresh organs, made transparent with 'acetic acid'. As a result he observed that the inner structure (parenchyma) is formed mainly by a varied number and size of rounded 'nodules' *(Klümpchen*), which can already be seen under low magnification of thinly spread specimens (Plate [Fig. 3]). Most possess a thick wall, which has externally a layer of conjunctive fibres where numerous cells with oblong dark-contoured nuclei are interspersed.

Plate. Figures depicting aspects of the carotid arteries, and the disassembled 'carotid gland' (Plate X – B of Luschka's paper).[15]
Fig. 1: a=common carotid, b=internal carotid, c=external carotid, d='carotid ganglion' [carotid body], carotid ligament; **Fig. 2:** a=common carotid, b=internal carotid, c=external carotid, d='carotid gland' split in two lateral halves, e=ligament of the 'carotid gland' implanted in the wall of the bifurcation site of the internal carotid artery; **Fig. 3**: 'nodule' [lobule] of the 'carotid gland' (amplified 200 times), displaying a=internal conjunctive stroma with interspersed oblong nuclei, bb= 'vesicles' filled with cells, nuclei and molecular masses [nerve bundle sectioned transversally], cc=larger 'vesicles' enclosing cells and smaller 'vesicles' [cell cluster], d=nerve-net with nearby eee=ganglionic cells; **Fig. 4:** 'tubule' near a group of rounds 'vesicles' filled with nuclei and cells [possible myelinated nerve bundles]; **Fig. 5:** isolated cells from a 'vesicle' [isolated gland cell]; Fig. 6: ganglionic cells enclosed in a thick sleeve; **Fig. 7:** group of ganglionic cells.

The glandular component, he writes, comprises two types of forms, rounded 'vesicles' (*Blasen*) and 'tubules' (*Schläuchen*). The 'vesicles' are spherical, or elongated, sometimes with the shape of a piston, or sandglass. The 'tubules' may be cylindrical, or with bulges, simple or forking, with unequal lengths, rarely with a lengthy course,variously curved, and inserted between the 'vesicles' without a definite order. The content of this structure sticks tightly to the wall (Plate [Fig. 4 and 5]).Observing the content of such preparations on thin slices 'in situ', previously hardened with 'chromic acid', varied shapes of the components appear. Some contain smaller 'vesicles' with very thin walls, enclosing forms that are in part delicate 'molecules' (*Molecüle*), some with dark contours and greasy shine, and in part are 'naked nuclei' (*nackte Kerne*), which usually have a rounded shape, some are uniform and clear, others granular, and most provided with a nucleolus (*Kernkörperchen*).[15] There are also cells (*Zellen*) of different shapes, most are oblong-round, or polygonal, or irregularly shaped. Sometimes, in some 'vesicles', are found cells which resemble a columnar epithelium, which at the free end show a kind of basal stratum. Some preparations with 'chromic acid' reveal 'conic cells' (*konische Zellen*) at the thicker end of which appear attachments that remind glued cilia. In the cells are found well-defined nuclei, close to which often are seen some larger, dark elementary granules, and lastly, the cell contents are finely granulated, rarely being so homogeneous that a hyaline appearance resulted. The arrangement of the cells is generally irregular.But often are seen 'vesicles' where the cells are pushed towards the periphery, spreading like an epithelium (Plate [Fig. 3]).[15] Additionally, he describes sparse 'ganglionic cells' (*Ganglienzellen*), provided with 'prolongations' [dendrites], and in continuity with 'nerve tubes' [axons], single or in small groups, and frequent 'apolar ganglionic cells' (*apolare Ganglienzellen*), isolated or in groups enclosed in a membranous covering (Plate [Fig. 6 and 7]).[14,15]

The organ has a rich arterial supply in part provided by direct small branches from the common carotid artery, arising from the bifurcation angle, and part from the surrounding spreading networks of the adventitia (Figure 2 and Plate [Fig. 1 and 2]). The vascular content of the organ is extraordinarily large. From the sturdier branches appear twigs that enter from all sides, spreading over the 'glandular clusters' or 'parenchymal-clusters' (*Parenchym-Klümpchen*), and forming inside the gland an intertwining meshwork, a very rich capillary net, around the glandular cells (Plate [Fig. 3]).[14,15]

Regarding the nerve supply, he describes that between the external and internal carotid arteries may be found, at the bifurcation angle, a very rich nervous net, the 'intercarotid plexus' (*plexus intercaroticus*), formed by a varied number of branches from the 'superior cervical ganglion' (*ganglion cervicale supremum*), filaments from the vagus trunk (and superior laryngeal branch), and glossopharyngeal nerve (Figure 2). From the 'plexus', fibres enter the core of the organ forming a net of delicate fibrils. The nerves may reach such a delicacy that they only consist of one or a few primitive fibers [Remak's]. The fine nerves have interspersed oblong nuclei, often longitudinally striped, or even band-like, identical to the so-called Remak's fibers [nerve fibres lacking a myelin, and enveloped by a sheath of Schwann cells]. There is also the perineurium on some nervous branches, which appears thick, what is noticeable on cross section, which contours often bear a resemblance to smaller 'vesicles'.[14,15]

Initially, regarding the organ, he concludes that in his view the formation is a 'sort of a ganglion' (*Ganglion eigener Art*)) or that it is not a ganglion in the usual sense, but a "...glandular organ associated to the cervical sympathetic..." (*...drüsenartiges, dem Halstheile des Sympathicus adjungirtes Organ...*). Later, he affirms that he has demonstrated the 'glandular nature' of the organ, and that it has the characteristics of a 'neural gland' (*Nervendrüse*).Finally, considering the place of its occurrence and its nature, he wrote that the 'intercarotid gland' may be designated 'carotid gland' (*glandula carotica*).[14,15]

COMMENTS

Here, the main features of the 'carotid body', and its nervous and vascular supply, as described by classic authors exposed in the text above, will be analysed, and interpreted in the light of present-day knowledge, based on the texts of recent publications,[1,2,3,4,5,6,7] in order to understand the meaning of these findings.

The 'carotid body' was first recognized and named by Taube (1743), and the interest about the organ proceeded until Luschka (1962) [and beyond], and in this period its existence was confirmed, acquiring different names. The authors recognized some macroscopic characteristics, as location, size, texture, colour, progressive identification of related nerves, from the superior cervical ganglion, the glossopharyngeal and vagus nerves, and their course to the carotid bifurcation and to the 'body', at last, not very far to the present-day knowledge.

On the other hand, the study of the microscopic structure suffered a delay, being described for the first time by Luschka (1862), more than a century after the discovery of the organ.[9,14,15] Such delay can be attributed to methodological problems, being opportune to remember that the basic histological methods, as fixation, embedding, sectioning, staining were not available before and at Luschka's time, as such processes have begun to appear, developing only later.[16,17,18] As a consequence results a great difficulty to interpret the microscopic findings in the light of present-day knowledge. Some described forms certainly are fated to remain without identification, considering that the fine structure studies were performed by observing fresh tissue, that submitted to procedures [not specified], applied to dried sections, specimens hardened in 'chromic acid', and preparations of fresh organs, thinly outspread, and made transparent with 'acetic acid'. Such procedures make difficult to adequately reveal and to distinguish among the varied cellular and fibrous components of the organ. Additionally, the presence of artifacts, due to the primitive techniques to study the organ, also represents a source of such difficulties.

Luschka tackle the subject in two publications, a book (*Die Anatomie des Menschen in Rücksicht auf die Bedürfnisse der praktischen Heilkunde 1.1*), and a paper (*Ueber die Drusenartige Natur des Sogenannteh Ganglion Intercaroticum*), both issued in the same year (1862).

He described, the then named 'intercarotid ganglion' (*Ganglion intercaroticum*) [according August Mayer], the overall structure, the cellular components, and the vascular and nervous supply of the organ that he considered a 'gland', a 'neural gland' (*Nervendrüse*), and renamed it to 'carotid gland' (*glandula carotica*).

The overall structure of the organ was inspected by compressing it between glass plates, or by examining thinly spread specimens, under low magnification[14,15] with a lens (loupe). Such procedure revealed rounded 'nodules' [lobules] of varied size mingled in fibrous tissue, most possessing a thick fibrous wall, and externally a layer of conjunctive fibres with countless cells with oblong dark-contoured nuclei (Plate [Fig. 3]).

This description is comparable to the present-day lobular structure ['nodules'] of the organ surrounded by conjunctive fibres and fibrocytes with its oblong nuclei.

The inner glandular composition (parenchyma) contains 'vesicles' (*Blasen*), spherical, or elongate, with a content that sticks tightly to the wall. Besides, they contain also 'tubules', which may be cylindrical, or with bulges, simple or forking, with unequal lengths, rarely with a lengthy course, variously curved, and inserted between the 'vesicles' without a definite order (Plate [Fig. 4 and 5]).

The 'vesicles' probably are clusters of cells that form the nodular (lobular) shape of the organ. The 'tubules' are difficult to identify but may stand for longitudinally cut nerve bundles or tangential view of blood vessels.

The parenchymal components comprise cells (*Zellen*), most oblong-round, or polygonal, or irregularly shaped, with a well-defined nucleus, the contents of which [cytoplasm] may be finely granulated, rarely being so homogeneous that a hyaline appearance resulted, and close to which are often seen some larger, dark elementary 'granules' [undetermined type of cells] (Plate [Fig. 3]).

It is possible to consider this description as elements compatible to the type I cells or 'principal cells', and possibly by type II cells or 'sustentacular'. These cells form clusters that are seen as 'vesicles'.

He also describes sparse 'ganglionic cells' (Ganglienzellen), provided with prolongations [dendrites], and in continuity with nerve tubes [axons], single or in small groups, and frequent 'apolar ganglionic cells' (apolare Ganglienzellen), isolated or in groups enclosed in a membranous covering (Plate [Fig. 6 and 7]).

The 'ganglionic' multipolar and the 'apolar' cells certainly represent neurons that are found inside the organ.

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Then he describes varied forms, as small 'vesicles' with very thin walls, enclosing delicate 'molecules', some with dark contours and greasy shine, part are 'naked nuclei', usually with rounded shape, parts uniform and clear, parts granular, and most provided with a nucleolus (Plate [Fig. 3]).

This interpretation is difficult, but the small 'vesicles' may represent transversally cut 'nerve fibres'.

The nerve supply is represented by the numerous fibres, originated from the 'intercarotid plexus', which enter the core of the organ, and there constitute a net of delicate fibrils, with interspersed oblong nuclei, often longitudinally striped, or even band-like, identical to the so-called Remak's fibers (Plate [Fig. 3]).

The identification is difficult, as the fibers are not properly stained, as already explained.However, the author's description represents fasciculi that enter and spread inside the organ, sectioned longitudinally and transversally, with nuclei of Schwann, and of perineural cells.

Concluding, it may be understood, that the description of the macroscopic features related to the carotid body, including location, extrinsic innervation, and vascular supply, provided by the cited authors, taken as a whole, is fairly satisfactory.

Regarding the microscopic findings, despite the great and admirable effort made by Luschka, may be viewed as frail, what can be ascribed to the technical limitations at the time.

Nevertheless, there is no doubt that Luschka and his forerunners provided the starting knowledge of the structure of the carotid body, and its innervation, although nothing was mentioned about its purpose. The studies that followed, after these first steps, revealed the structural details of the organ with superior detail, as well as its functional importance.[19,20,21]

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