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Review

Peripheral chemoreceptors: postnatal development and cytochemical findings in Sudden Infant Death Syndrome

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Summary. The aim of the present study is to give a review of the postnatal development of peripheral chemoreceptors - carotid body, paraganglia, and pulmonary neuroendocrine cells (PNEC) - with implications in Sudden Infant Death Syndrome (SIDS). In the postnatal period, the hypoxic chemosensitivity of the carotid body gradually develops. Changes include proliferation of type I and II cells, increased numbers of dense core vesicles and K^+ channels, and modifications of neurotransmitter/neuromodulator and receptor expression. Chromaffin paraganglia show increased expression of nitric oxide synthase and neuropeptides, and increased innervation. Innervation of PNEC develops fully only in the first postnatal period, after which their density falls. The neuropeptides produced by PNEC also changes, with increased expression of calcitonin gene-related peptide and neuropeptide YY and reduced expression of calcitonin and gastrin-releasing peptide.

Most of the findings in the carotid body of SIDS victims, i.e., decrease in type I cells and dense cytoplasmic granules, and increase in progenitor cells, indicates immaturity of the carotid body, which may play a role in SIDS in the form of underlying biologic vulnerability. Aorticopulmonary paraganglia hyperplasia and increase of PNEC are also found in SIDS, and may be epiphenomena of alterations of the respiratory function with a pathogenetical role in SIDS. A comprehensive view of the pathogenesis of SIDS should also arise from the integration of peripheral chemoreceptors findings with neuro- and cardiopathologic ones.

Key words: Carotid body, Paraganglia, Pulmonary neuroendocrine cells, Sudden infant death syndrome, Autonomic nervous system

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Introduction

Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including complete necroscopy, examination of the death scene, and review of the clinical history (Willinger et al., 1991). SIDS is the commonest form of death in infancy, striking about 1 out of every 700-1,000 infants per year (Centers for Disease Control and Prevention, 1996).

Research on the pathogenesis of SIDS has mainly focused on three causative factors, i.e., the respiratory (apnea, suffocation), the cardiac (arrhythmia), and the visceral diskinesis (spasm, reflux) theses. However, a significant interplay among the neurogenic factors in all these hypotheses has been suggested (Rossi, 1999; Matturri et al., 2005a). A triple-risk model of SIDS has also been proposed, postulating an underlying biologic vulnerability to exogenous stressors or triggering factors in a critical developmental period (Filiano and Kinney, 1994; Ottaviani et al., 2005). Hypoplasia and neuronal immaturity of brain stem structures involved in central chemoception and cardiorespiratory regulation, such as the medullary arcuate nucleus (Matturri et al., 2004; 2005a), parabrachial/Kölliker-Fuse complex (Lavezzi et al., 2004), respiratory reticular formation (Matturri et al., 2005a,b), motor vagal nuclei (Macchi et al., 2002) and hypoglossal nucleus (Ottaviani et al., 2006), have been described as possible morphological substrates for SIDS.

Peripheral chemoreceptors play an important role in regulating cardiorespiratory functions, and hypotheses of the immaturity of reflexes triggered by peripheral chemoreceptors in SIDS have also been made in the literature. The typical arterial peripheral chemoreceptor is the *carotid body*. However, tissues similar to this structure have also been described in various other sites and are defined as *paraganglia* (aorticopulmonary, vagal). Chemosensitive functions have also been ascribed to *neuroendocrine cells* located in the

epithelium of medium and small airways in the lung, although they respond to gases of inspired air more than blood. Many animal and human studies indicate that the development of the peripheral chemoreceptors is also protracted in the postnatal period. However, previous authors restricted their investigations to specific tissue, cellular or molecular changes in single chemoreceptor types. A comprehensive review of the findings regarding postnatal development of all these peripheral chemoreceptors is still lacking. Hypotheses of immaturity of reflexes triggered by peripheral chemoreceptors in SIDS have also been proposed and investigated in the literature, but a comprehensive overview of these studies is not yet available.

The aim of the present paper is to give a comprehensive review of structural changes in peripheral chemoreceptors in postnatal development and of cytochemical findings in SIDS. Considerations about future prospects of research into these topics are also made.

Carotid body

Postnatal development

The carotid body is an arterial chemoreceptor, sensitive to reductions in partial blood oxygen pressure and pH and to increases in partial CO_2 pressure, the stimulation of which induces increases in ventilatory frequency and volume (Belmonte and Gonzalez, 1983), through activation of the bulbar respiratory centres (Vardhan et al., 1993). It is also stimulated by a fall in arterial pressure, with peripheral vasoconstriction and bradycardia as a response (Eyzaguirre and Zapata, 1984).

The carotid body is a single, ovoid tissue mass, situated at the carotid bifurcation (Smith et al., 1982), composed of lobules separated by connective tissue (Fig. 1A), into which afferent fibres of the glosso-pharyngeal nerve, arising from the petrosal ganglion, occur (Pallot, 1987). The lobules are organised in clusters containing cells belonging to two separate populations: chief (or type I) cells, in turn separated into light, dark and pyknotic, and sustentacular (or type II) cells, at the edges of the clusters (Verna, 1979; Pallot et al., 1986) (Fig. 1B,C). Post-ganglionic sympathetic nerve fibres from the superior cervical ganglion are present, innervating blood vessels and type I cells (Verna, 1997). Preganglionic parasympathetic and sympathetic fibres also reach ganglionic cells, which are either isolated or found in small groups near the surface of the carotid body (McDonald and Mitchell, 1975; Standring et al., 2005). Axons from the ganglion cells innervate the blood vessels, the parasympathetic axons being vasodilator (Biscoe et al., 1969) and the sympathetic vasoconstrictor (Purves, 1970).

Glomic cells store many neurotransmitters or neuromodulators, such as dopamine, serotonin, noradrenaline, adrenaline, acetylcholine, adenosine, met- and leu-enkephalins, neuropeptide Y, CGRP, galanin, endothelins, bombesin, NO (Gonzalez et al., 1994; Verna, 1997; Kusakabe et al., 2003; Bairam and Carroll, 2005). Our research group also recently identified adrenomedullin in human chief cells (Porzionato et al., 2006) (Fig. 1D,E).

Although some authors (McDonald and Mitchell, 1975) proposed that afferent glossopharyngeal nerve endings are the true chemoreceptors, type I cells are nowadays generally considered to be the real chemoreceptors of the carotid body (Gonzalez et al., 1994; Verna, 1997; Wang and Bisgard, 2005).

The carotid body develops as a condensation from the mesenchyme of the third pharyngeal arch. As regards its functional development, this chemoreceptor does not contribute much to breathing during foetal life, in spite of a hypoxia level of about 25 torr (Blanco et al., 1984), and its activity is not necessary in order to establish rhythmic breathing at birth (Jansen et al., 1981). In the following postnatal period a gradual increase in hypoxic chemosensitivity develops, with a change in the hypoxic threshold to 55 torr (Blanco et al., 1984, 1988; Gauda et al., 2004) and an increase in the slope of the hypoxic stimulus response curve (Blanco et al., 1984; Bamford et al., 1999; Kholwadwala and Donnelly, 1992; Gauda et al., 2004).

Postnatal changes in the peripheral chemoreceptors are listed in Table 1. In adult cat, a three-fold increase in the volume of the carotid body has been described with respect to newborns (Clarke and Daly, 1985; Clarke et al., 1990). Some authors found very few mitoses in the carotid body of newborn kitten (Clarke and Daly, 1985), rat (von Dalnok and Menssen, 1986) and human (Heath et al., 1990), assuming improbable postnatal increase in the number of type I cells. However, it has been found that type I cells from newborn rats divide in culture (Fishman and Schaffner, 1984; Nurse and Fearon, 2002) and Wang and Bisgard (2005) identified bromo-deoxyuridine-labelled type I cells in newborn rats, providing evidence of proliferation of type I cells in the postnatal period.

Some cellular and molecular changes associated with postnatal increase in hypoxic chemosensitivity have been identified in the higher density of K^+-channels (Peers and O'Donnell, 1990), a greater rise in intracellular Ca^{2+} levels in response to hypoxia (Sterni et al., 1995; Bamford et al., 1999) and changes in neurotransmitter profile (Gauda et al., 1996, 2000, 2004). Immunohistochemical and hybridisation studies have shown increased neuropeptide Y expression (Oomori et al., 1991) and reduced tyrosine hydroxilase (Holgert et al., 1995; Sterni et al., 1995; Bamford et al., 1999), cannabinoid 1 (McLemore et al., 2004) and dopamine 2 receptor expression (Holgert et al., 1995; Sterni et al., 1995; Bamford et al., 1999). In one of our preceding studies, involving both immunohistochemistry and immunofluorescence, we found increased expression of adrenomedullin in adult subjects with respect to foetuses of 21-25 weeks of gestational age (Porzionato et

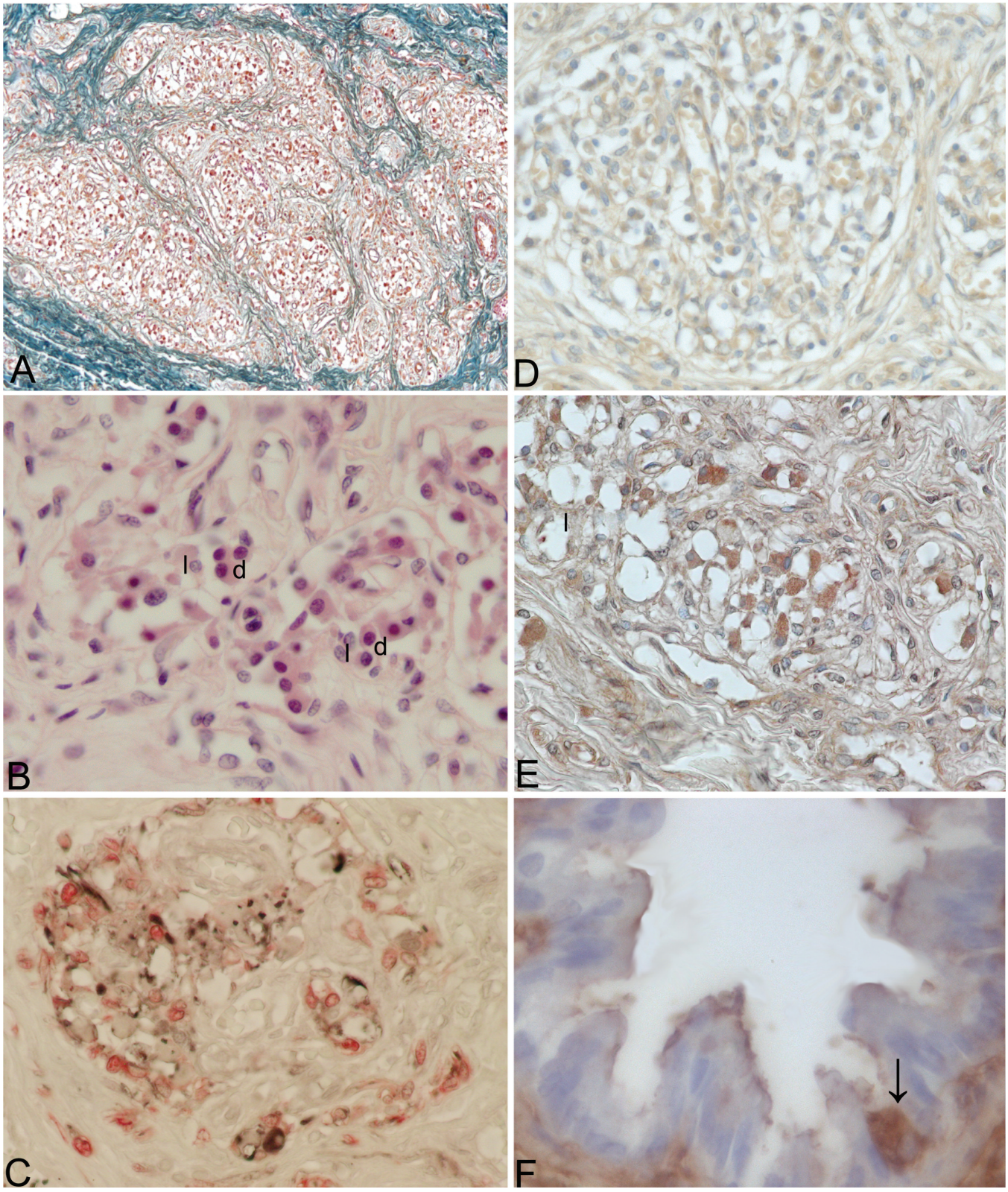

Fig. 1.A. Longitudinal section of human carotid body, showing parenchymal and connective components (azan-Mallory; original magnification, x 10). **B.** Section of carotid body showing light (l) and dark (d) cells (original magnification x 63). **C.** Double-labelling immunohistochemistry with anti-neurone-specific enolase (black stain) and anti-S100 (red stain) antibodies, showing type I and II cells, respectively (original magnification x 40). **D, E.**Sections of human carotid body immunostained for adrenomedullin displaying higher percentage of immunostained type I cells in adult subject (E; original magnification x 63) with respect to a foetus of gestational age of 170 days (D; original magnification x 40). **F.** Pulmonary neuroendocrine cell (arrow) stained with immunohistochemistry anti-chromogranin A in an intralobular bronchiole (original magnification x 100).

Table 1. Postnatal changes in peripheral chemoreceptors.

Changes	Species	References
CAROTID BODY		
Proliferation of type I cells	Rat	Wang and Bisgard, 2005
Improb. postnatal increase in type I cells	Cat Rat Human	Clarke and Daly, 1985 Von Dalnok and Menssen, 1986 Heath et al., 1990
↑ dense core vesicles in type I cells	Rat	Von Dalnok and Menssen, 1986
↑ K^+ channels	Rat	Peers and O'Donnell, 1990
↑ rise in $[Ca^{2+}]i$ in response to hypoxia	Rabbit Rat	Sterni et al., 1995 Bamford et al., 1999
↑ neuropeptide Y	Rat	Oomori et al., 1991
↓ tyrosine hydroxylase	Rabbit Rat Rat	Sterni et al., 1995 Holgert et al., 1995 Bamford et al., 1999
↓ cannabinoid 1 receptors	Rat	McLemore et al., 2004
↓ dopamine 2 receptors	Rabbit Rat Rat	Sterni et al., 1995 Holgert et al., 1995 Bamford et al., 1999
↑ adrenomedullin	Human	Porzionato et al., 2006
↑ endothelial cells	Rat	Wang and Bisgard, 2005
↑ type II cells	Rat	Wang and Bisgard, 2005
↑ synapses between type I and II cells	Rat	Kondo and Iwasa, 1996
↑ Schwann cells of nerve fibres	Rat	Wang and Bisgard, 2005
PARAGANGLIA		
Changes	Species	References
Enlargement	Human	Plenat et al., 1988
↑ vascularization (during gestational age)	Human	Dixon et al., 1998
↑ nitric oxide synthase	Human	Dixon et al., 1998
↑ neuropeptides	Human	Dixon et al., 1998
↑ innervation	Human	Dixon et al., 1992
Changes in relationships nerve fibres/paraganglion cells	Human	Dixon et al., 1998
LUNG NEUROENDOCRINE CELLS		
Changes	Species	References
↓ lung NEB	Human Human Human	Cutz et al., 1984 Spindel et al., 1987 Perrin et al., 1991
↑ total number of NEB	Hamster	Van den Steen (1997)
↓ density of NEB	Hamster	Van den Steen (1997)
↑ NEB opening to the airway lumen	Hamster	Van den Steen (1997)
↓ dying or death PNEC	Hamster	Van den Steen (1997)
↓ "closed type" cells	Human	Sunday, 1997 Pan et al., 2006
↑ innervation of NEB by CGRP positive nerve fibres	Rat	Cadieux et al., 1986 Sorokin et al., 1997
↑ innervation of NEB	Hamster	McDowell et al., 1994a,b
First postnatal wave of CGRP positive PNEC Second postnatal wave of Peptide YY positive PNEC	Human	McDowell et al., 1994a,b
↓ GRP receptor gene expression	Baboon	Emanuel et al., 1999
↓ calcitonin and GRP immunoreactivity	Human	Nakagawa et al., 1994

al., 2006) (Fig. 1D,E). In rats, an increase in the number of dense core vesicles of type I cells has also been found by the end of the first postnatal week (von Dalnok and Menssen, 1986).

Proliferation of endothelial cells and type II cells (Wang and Bisgard, 2005) and increased number of synapses between type I and II cells (Kondo and Iwasa, 1996) have also been described in newborn rats. As regards innervation of glomic cells, some authors have found proliferation of Schwann cells lining peripheral nerve fibres (Wang and Bisgard, 2005) and glial and Schwann cells in the petrosal and superior cervical ganglia of rats (Wang and Bisgard, 2005; Lemke, 2001).

Postnatal changes in the carotid body may be ascribed partly to the role of growth factors, such as brain-derived neurotrophic factor (BDNF) and glial cell-line derived neurotrophic factor (GDNF), produced by type I cells (Hertzberg et al., 1994; Erickson et al., 2001; Wang and Bisgard, 2005). Trk B, which is the receptor of BDNF, is located in both type I cells and chemoafferent neurons, suggesting that it has autocrine and paracrine functions. Ret, which is the receptor of GDNF, is instead only found in petrosal sensory neurons and nerve fibres (Wang and Bisgard, 2005).

Carotid body in SIDS

Cytochemical findings in SIDS are listed in Table 2. In the literature, carotid body volume and cell number anomalies have been described in cases of SIDS. Naeye et al. (1976) found subnormal or enlarged volumes of glomic cells in 63% and 23%, respectively, of SIDS

Table 2. Findings in peripheral chemoreceptors of SIDS victims.

CAROTID BODY	
Findings	References
↓ volume of glomic cells	Naeye et al., 1976 Cole et al., 1979
↑ volume of glomic cells	Naeye et al., 1976
↓ number of glomic cells	Cole et al., 1979
↓ type I cells - ↑ type II cells	Heath et al., 1990 Cutz et al., 1997 (congenital central hypoventilation)
↓ carotid body volume	Cutz et al., 1997 (congenital central hypoventilation) [not confirmed in SIDS by Dinsdale et al., 1977 Perrin et al., 1984 Lack et al., 1986]
↑ progenitor cells	Pavai et al., 2005
↓ dense cytoplasmic granules	Cole et al., 1979 Cutz et al., 1997 (congenital central hypoventilation) [not confirmed by Perrin et al., 1984 Lack et al., 1986]
↑ dopamine content	Perrin et al., 1984b [not confirmed by Lack et al., 1986]
↑ noradrenaline content	Perrin et al., 1984b [not confirmed by Lack et al., 1986]
PARAGANGLIA	
Changes	References
Aorticopulmonary paraganglia hyperplasia	Matturri et al., 1992 Matturri et al., 1993 Ramos et al., 1998
No findings in vagal paraganglia	Lack, 1989
LUNG NEUROENDOCRINE CELLS	
Changes	References
↑ lung neuroendocrine cells and bodies	Cutz et al., 1988 Gillan et al., 1989 Perrin et al., 1991 Cutz et al., 1996 Aita et al., 2000
↑ bombesin-positive NEB	Cutz et al., 1997 (congenital central hypoventilation)

cases. Evidence of antecedent chronic alveolar hypoxia and hypoxemia was more severe in subjects with enlarged volumes. Congenital anomalies of the parathyroids have also been reported in SIDS, so that it has been suggested that developmental arrest of the third arch may contribute pathogenetically to SIDS (Geertinger, 1976). The volume of glomic tissue in SIDS cases was also evaluated by Dinsdale et al. (1977) who, however, did not find increases in the size of the carotid body in the majority of cases. They only reported the probability that enlargement occurs in some children dying at the age of one year or older. Cole et al. (1979) reported a reduction in cell number and volume in four cases of SIDS, but in the 1980s two papers by different research groups (Perrin et al., 1984a; Lack et al., 1986) excluded differences in weight or functional area of the carotid body in SIDS. In spite of this, it is worth noting that reduced carotid body volume has also been reported in two cases of congenital central hypoventilation syndrome, a condition related to SIDS (Cutz et al., 1997).

Heath et al. (1990) described the absence of dark and light cells with predominant sustentacular and progenitor cells. Reduction of chief cells with an increased number of sustentacular cells has also been reported by Cutz et al. (1997) in congenital central hypoventilation syndrome. Instead, a significantly higher number of progenitor cells in SIDS victims than in controls has recently been reported (Pavai et al., 2005).

Other parameters evaluated in the carotid body of SIDS victims are distribution, and number and size of cytoplasmic granules in chief cells. Cole et al. (1979) found a marked reduction or absence of dense cytoplasmic granules, as did Cutz et al. (1997) in congenital central hypoventilation syndrome. These data, however, were not confirmed by Perrin et al. (1984a) or Lack et al. (1986).

In the literature, there are few data regarding the content of neurotransmitters and neuromodulators in the carotid body of SIDS victims. It has been reported that such carotid bodies contain ten- and three-fold higher concentrations of dopamine and noradrenaline, respectively (Perrin et al., 1984b). It was suggested that elevated levels of catecholamines compromise the normal chemoreception function of the carotid body, with particular reference to the ventilatory response to hypoxia. With the exception of one paper (Lack et al., 1986) which did not confirm differences in catecholaminergic content between SIDS victims and controls, no other studies on this topic have been performed.

In human infants, many authors have found that exposure to tobacco smoke alters hypoxic arousal and ventilatory responses (Lewis and Bosque, 1995; Ueda et al., 1999; Gauda et al., 2004). Experimental studies on animals also confirmed such findings in prenatal tobacco smoke exposure. In newborn rats, reduction of hypoxic ventilation (St-John and Leiter, 1999) and autoresuscitation after repeated asphyxial stimuli (Fewell and Smith, 1998) were found. Robinson et al. (2002) reported the higher frequency of spontaneous and post-hypoxic apnoea in newborn mice. Hafstrom et al. (2002) reported reduced ventilatory and arousal responses to hypoxia during sleep in newborn lambs. Peripheral chemoreceptors play a major role in regulation of these physiological responses, so that all these findings support the hypothesis that prenatal nicotine alters the function of these chemoreceptors (Gauda et al., 2004). In spite of the above-mentioned functional studies on respiratory regulation and peripheral chemoreception after prenatal nicotine exposure, little is known about the cellular and molecular mechanisms involved. In the carotid body of newborn rats, increases in tyrosine hydroxylase and dopamine ß-hydroxylase mRNA have been found (Holgert et al., 1995; Gauda et al., 2001).

The literature contains experimental reports on animals which investigate the effect of postnatal exposure to hypoxia and hyperoxia on the carotid body. Wang and Bisgard (2005) revealed increases in BrdU-positive and total type I cells after one week of hypoxia (12% O_2), while hyperoxia (60% O_2) produced decreases in proliferating and total type I cells for a corresponding time interval. Increases and decreases in tyrosine hydroxylase and sinaptophysin were also found in type I cells after hypoxia and hyperoxia, respectively (Wang et al., 2003, 2004). Erickson et al. (1998) found a decreased number of unmyelinated sensory nerve fibres and of tyrosine hydroxylase-positive stained neurons in the petrosal ganglion following exposure to hyperoxia for the first four postnatal weeks, whereas no such changes were observed in the vagal nodose ganglion, demonstrating that the effect of high oxygen levels was specific to sensory neurones in the carotid body afferent pathway.

Paraganglia

Postnatal development

Penitschka (1931) and Nonidez (1935) were the first authors to identify carotid body-like structures in the vicinity of the aortic arch, which they called paraganglion aorticum supracardiale and aortic body, respectively. Comroe (1939) confirmed the presence of a large cell mass in the aortic adventitia and reported reflex changes in respiration and cardiovascular activity similar to those evoked from the carotid body in response to chemical stimulation. The term aortic bodies was then adopted for all paraganglia in the aortic arch region (Howe, 1956), but aortic bodies were also identified in the adventitia of the ascending aorta (Becker, 1966) and in the ascending aortic fold (Lebona, 1993). In addition, such structures were also found in the walls of the pulmonary trunk and bifurcation and in the connective tissue between the aorta and pulmonary arteries in both birds (Taha and King, 1986) and mammals (Mauri et al., 1989; Matturri et al., 1992,

1993; Ramos et al, 1998). Thus, the terms aorticopulmonary bodies or paraganglia were used to indicate both intramural and extramural bodies of the aorticopulmonary region. It is now accepted that they function as chemoreceptors, being stimulated by decreases in blood P_{O2} and pH and by increases in P_{CO2}. The microscopic anatomy of the aorticopulmonary paraganglia is very similar to that of the carotid bodies, with cell nests made up of type I or chief cells, larger and oval, and type II or sustentacular cells, smaller and spindle-shaped (Lebona, 1993; Taha and King, 1986). As regards embryonic development, the aortic bodies develop from the mesenchyme of the fourth and sixth pharyngeal arches (Standring et al., 2005).

Paraganglionic cell clusters composed of round chief cells and elongated sustentacular cells have also been described within or adjacent to the vagal trunk/ganglia and have been called intra- and juxtavagal paraganglia, respectively. They were first described by Muratori (1932) in birds, and by White (1935) in humans. In the latter, they have mainly been identified in the superior and inferior vagal ganglia and within or adjacent to the first centimeters of the trunk distal to the inferior ganglion (White, 1935; Lattes, 1950; Birrell, 1953; Lack, 1978). However, Plenat at al. (1988) identified vagal paraganglia in the cervical vagus nerve, far below the inferior vagal ganglion, and also in the inferior laryngeal nerve. The distribution of vagal paraganglia is more extensive in rodents, where they are also found associated with the abdominal branches of the vagus nerve (Goormaghtigh, 1936; Hollingshead, 1941; Gabella and Pease, 1973; Mascarro and Yates, 1975). Although most vagal paraganglia appear as microscopic islets of neuroendocrine tissue virtually identical to the carotid body, together with chief and sustentacular cells, others resemble small autonomic ganglia (Kummer and Neuhuber, 1989). It has been suggested that vagal paraganglia may also play a role in peripheral chemoreception (Hollingshead, 1941; Deane et al., 1975; Howe and Pack, 1977; Howe et al., 1981; Kummer et al., 1989; Kummer and Neuhuber, 1989; Lack, 1989). Andrews et al. (1971) demonstrated the presence of sensory units with chemoreceptor-like activity associated with abdominal vagal paraganglia. The chemoreceptor activity of abdominal vagal paraganglia was also supported by a structure indistinguishable from rat carotid body (Deane et al., 1975; Morgan et al., 1976; Howe and Pack, 1977). Lack (1978) reported increases in the number and size of the vagal paraganglia and hyperplasia of chief cells in chronic hypoxia, supporting this role. Little is known about the postnatal development of vagal paraganglia. Plenat et al. (1988) only reported that the paraganglia were smaller in newborns than in adults, although with similar structure.
The term paraganglia also refers to large clusters of extra-adrenal chromaffin tissue containing catecholamines, most frequently located in the retroperitoneal space (Zuckerkandl, 1901) or associated with the urinary bladder (Thompson and Gosling, 1976; Hervonen et al., 1976; Dixon et al., 1998). The description of two types of paraganglia, chromaffin and non-chromaffin, had already been proposed by Terni (1924, 1927) and Kohn (1929). Chromaffin paraganglia are not considered to have a chemosentitive function. Although they can release catecholamines in response to severe hypoxia (Hervonen and Korkala, 1972), it is not clear whether this response is direct or mediated through nerve fibres (Hervonen et al., 1985). However, their postnatal development has been studied in humans. Dixon et al. (1998) found that small clusters of paraganglion cells migrate from the adventitia of the urinary bladder and prostate gland into the bladder wall. Vascularisation of the paraganglia also increases with increasing gestational age (Dixon et al., 1998). The expression of many neuropeptides and nitric oxide synthase (NOS) also increases during foetal and postnatal periods (Dixon et al., 1998). The relationships between nerve fibres and paraganglia also change during foetal and postnatal development. Foetal paraganglia are associated with relatively few nerve fibres, whereas relatively rich innervation may be found in the postnatal period, mainly composed of VIP-immunoreactive nerve fibres (Dixon et al., 1992). Only in late foetal and early postnatal tissues can sensory corpuscles be detected in pelvic paraganglia; in the first few months of the postnatal period, the corpuscles separate from the paraganglia (Dixon et al., 1998).

Paraganglia in SIDS

Aorticopulmonary paraganglia hyperplasia and mild inflammation were first noted by Matturri et al. (1992, 1993) in a male sixty-day-old infant diagnosed as an SIDS victim. A morphometric study on serial sections of the aorticopulmonary paraganglia was then performed with an image analyser. Aorticopulmonary paraganglia hyperplasia, characterised by an increase in number, mean lobule diameter and total glomic tissue volume, was found in 23.8% of SIDS victims with respect to age-matched controls (Ramos et al., 1998). These findings may reflect the abnormal role of the aorticopulmonary paraganglia, as chemoreceptors, in cardiovascular regulation (Matturri et al., 1992, 2005a; Ramos et al., 1998).

Conversely, Lack (1989), using a combined step and serial sectioning technique, did not find significant differences between SIDS and non-SIDS with regard to microanatomy, number, distribution and size of vagal body paraganglia.

Lung neuroendocrine cells

Postnatal development

The epithelium of medium and small airways contains neuroendocrine cells (PNEC) (Fig. 1F) which may group in neuroepithelial bodies (NEB). These cells may contain a series of biologically active substances,

i.e., serotonin (Lauweryns and Cokelaere, 1973, Lauweryns et al., 1977), calcitonin, calcitonin gene-related peptide (CGRP), peptide YY (McDowell et al., 1994a,b), chromogranin A (Lauweryns et al., 1987), pancreastatin (Seldeslagh and Lauweryns, 1993), cholecystokinin, somatostatin (Balaguer et al., 1992), endothelin, helodermin (Van Lommel, 2001), and gastrin-releasing peptide (GRP), a member of the bombesin-like peptide family (Wharton et al., 1978; Track and Cutz, 1982; Spindel et al., 1987). ATP has also been hypothesised as one of the neurotransmitters of NEB (Brouns et al., 2000). CGRP and GRP are the major neuropeptides produced in rodents and humans, respectively (Li et al., 1994).

NEB are predominantly innervated by afferent sensory nerve fibres, but also receive efferent fibres. In particular, three systems of afferent nerve fibres have been identified in rat lung. There is a vagal myelinated component, originating in the nodose ganglion, which shows immunoreactivity for calbindin and P2X3 purinoreceptors. A second sensory system consists of unmyelinated substance P/CGRP immunoreactive fibres, originating in the dorsal root ganglia. A third system of nitrergic nerve terminals originating from intrinsic neurons has also been identified. It is estimated that 40-50% of NEB receive purinergic innervation, 56% CGRP-immunoreactive nerve fibres, and 9-10% nitrergic terminals (Brouns et al., 2000, 2002, 2003). However, not all NEB show innervation in adult rat (Larson et al., 2003). Recent evidence also supports the innervation of solitary PNEC in rabbit and human (Pan et al., 2004; Weichselbaum et al., 2005). Stimulation of NEB may trigger two kinds of responses in the sensory nerves, transmission of the sensitive stimulus to the central nervous system, and local release of CGRP from axons by exocytosis. The release of CGRP from axons may serve to extend the zone of influence of NEB without first requiring signals to reach the central nervous system (Keith et al., 1991; Sorokin et al., 1997). Another mode of amplification of the action of NEB has been suggested in connection with other PNEC via fine submucosal nerve fibres (Pan et al., 2004).

Two different types of PNEC have been identified in human foetal lungs: "open type", showing a flask shape with cytoplasmic processes reaching the airway lumen, and "closed type", with elongated dendritic-like cytoplasmic processes along the basement membrane, without luminal contact. The closed type has been identified only in foetal or neonatal lungs (Sunday, 1997; Pan et al., 2006).

A dual role has been attributed to PNEC with reference to the stage of development: they may modulate lung growth and differentiation during early stages of lung organogenesis, and play a role as chemoreceptors in the first postnatal period (Sorokin and Hoyt, 1993). Many studies confirm the chemosensitive function of these cells. Increased exocytosis and decreased amine content were found in newborn rabbits after acute hypoxia (Lauweryns and Cokelaere, 1973; Lauweryns et al., 1978), together with increasing synaptic activity in sensory vagal fibres connecting with these cells (Lauweryns and van Lommel, 1982). Modulation by oxygen of the serotonin content of pulmonary NEB cells *in vitro* was also reported (Cutz et al., 1990). It has been pointed out that O_2 chemosensitivity in NEB is mediated by a plasma membrane-bound NADPH oxidase which, in response to hypoxia, inhibits K^+ channels producing depolarisation and neurosecretion (Nurse et al., 2006). It has been suggested that, while the carotid body monitors blood gases, NEB directly respond to changes in inspired air gases (Hanson, 1986, 1987). In this sense, lung chemoreceptors would complement rather than duplicate carotid body activity (Cutz and Jackson, 1999). Moreover, unlike the carotid body, NEB cells respond to acute hypoxia, but do not seem to respond to hypercapnia (Lauweryns et al., 1977, 1990; Cutz et al., 1993; Cutz and Jackson, 1999). It has been estimated that, in hamster, NEB represent a mass of chemosensitive cells and afferent nerves larger than the carotid bodies, indicating the significant physiological role of these cells, at least in the early postnatal period (Sorokin and Hoyt, 1990; Bolle et al., 1999). Newborn mice with a disruption of the Achaete-scute-homolog-1 gene have no PNEC and die about 12 hours after birth, due to hypoventilation and severe anomalies of the central nervous system (Guillemot et al., 1993; Borges et al., 1997). It has been hypothesised that lack of PNEC chemoreception may play a role in determining the fatal hypoventilation (Linnoila, 2006).

PNEC are the first cells to differentiate from endodermal precursors in the respiratory epithelium. In humans, PNEC and NEB can be detected at 8 and 12 weeks of gestation, respectively (Linnoila, 2006). At first, these cells differentiate in the larynx and upper trachea, and then expand centrifugally into the pulmonary airways. Three different waves of differentiation have been identified in hamsters. The first develops prenatally and gives rise to the main population of PNEC, made up of cells colocalising immuno-reactivity for serotonin, CGRP and, less frequently, calcitonin. The second developmental wave begins in the first week after birth, and produces solitary PNEC in the larynx and trachea, positive for CGRP, partly for calcitonin but not for serotonin. The third one is composed of postnatally developed cells, immunoreactive for peptide YY but not for CGRP, calcitonin and serotonin, occurring as single cells or as NEB in the alveoli (McDowell et al., 1994a,b). In baboons, Emanuel et al. (1999) found that GRP-receptor gene expression showed maximal levels on ED160 and then became undetectable after birth. Postnatal changes in the substances produced by PNEC have also been found in humans. Nakagawa et al. (1994) reported a decrease in calcitonin and GRP immunoreactivity in older infants, but no changes in chromogranin A immunoreactivity. PNEC reach a maximum at birth and then diminish in number postnatally (Cutz et al., 1984;

Spindel et al., 1987; Perrin et al., 1991), supporting the hypothesis that these cells may be involved in lung development and neonatal adaptation (Perrin et al., 1991). However, it has also been suggested that the postnatal decrease in PNEC is due to a "dilutional effect" for lung growth (Gosney, 1993). In hamsters, Van den Steen et al. (1997) found that the total number of NEB doubled from 14 days to 2.5 months although, considering constant surface areas, a consistent decrease was revealed. Increased numbers of NEB opening to the airway lumen and of the proportion of alveolar NEB were also found with age. It has also been reported that postnatally PNEC may still grow in number, as postnatal mitoses are observed in the red-eared turtle (Scheuermann, 1987), kittens (Van Lommel and Lauweryns, 1993) and adult hamsters (Sorokin and Hoyt, 1989). Only in neonate hamsters were immune-competent cells found in the vicinity of NEB, together with dying or dead cells (Van den Steen et al., 1997).

Pre- and postnatal development of sensory innervation of PNEC has also been studied. In rats, innervation of NEB by CGRP immunostained nerve fibres mainly develops during the first four postnatal weeks, whereas innervation by PGP 9.5-positive fibres is already clearly detectable during prenatal stages (Cadieux et al., 1986; Sorokin et al., 1997). The development of innervation of NEB in hamsters also shows a similar pattern (McDowell et al., 1994a,b). However, it has also been reported that sensory innervation of the NEB develops earlier than sensory innervation of the carotid body (Bolle et al., 2000), suggesting the very important contribution to adaptation to air breathing at birth, when carotid body function is relatively immature (Van Lommel, 2001; Pan et al., 2004). It has been hypothesised that innervation of PNEC may be guided by neurotrophic factors, such as glial-derived neurotrophic factor (GDNF), secreted by the same neuroendocrine cells (Pan et al., 2004).

Lung neuroendocrine cells in SIDS

Increased numbers of PNEC and NEB have been found in the lungs of SIDS victims with respect to age-matched controls (Cutz et al., 1988, 1996; Gillan et al., 1989; Perrin et al., 1991; Aita et al., 2000). The etiology of NEB hyperplasia in the lungs of SIDS victims has mainly been ascribed to chronic hypoxia or developmental delay (Cutz and Jackson, 1999). Airway inflammation, which is found in up to 30% of SIDS victims, may be another factor (Cutz and Jackson, 1999). It was also found that SIDS infants born to smoking mothers showed a higher number of PNEC with respect to other SIDS victims whose mothers were non-smokers, although NEB size and frequency did not significantly differ between the two groups (Cutz et al., 1996). Chen et al. (1987) had previously found increased size of NEB in humans exposed to maternal smoking. Experimental studies on animals have also evaluated the role of prenatal nicotine exposure. Keith and Cary (1988) confirmed stimulation of NEB growth in rodents. Sekhon et al. (1999) found increased size and number of NEB and decreased number of solitary PNEC in monkeys, suggesting mitogenesis stimulation in already differentiated PNEC, more than neuroendocrine differentiation of new cells. All these studies indicate that maternal smoking potentiates hyperplasia of the pulmonary neuroendocrine cell system in the lung.

Chronic hypoxia in both rodents and humans also causes NEB hyperplasia (Dhillon et al., 1984; Pack et al., 1986; Van Lommel et al., 1999) and a two-fold increase of frequency and size of NEB immunostained for bombesin was also found in two cases of congenital central hypoventilation syndrome (Cutz et al., 1997). In these cases, hypoplasia of the carotid bodies was also present, suggesting the compensatory significance to hyperplasia of airway chemoreceptors (Cutz et al., 1997). Wistar rats subjected to hypoxia for 1-3 weeks showed elevated levels of intracellular CGRP, without changes in NEB cell numbers (Pack et al., 1986). However, PNEC hyperplasia has also been reported, due to inflammatory or fibrotic noxae (Linnoila, 2006), and in bronchopulmonary dysplasia (Cutz et al., 1984). Conversely, in hyaline membrane disease, a reduced number of NEB has been reported (Cutz et al., 1984).

Proliferation of PNEC through exposure to nicotine or hypoxia may enhance the release of bioactive substances, alter pulmonary vaso- and bronchomotor tone, and induce proliferative effects (Van Lommel, 2001). Serotonin and CGRP have vasoconstrictor and vasodilator properties, respectively. Some clinical manifestations of bronchopulmonary dysplasia, such as pulmonary hypertension, higher airway reactivity and increased apnea episodes, have been ascribed to hyperplasia of NEB and increases in their mediators (Johnson and Georgieff, 1989). It is also of interest to note that bronchopulmonary dysplasia is also associated with increased incidence of sudden unexpected death (Cutz et al., 1984).

Conclusive remarks and future prospects

Findings in peripheral chemoreceptors of SIDS victims have to be evaluated with regard to their value in the cause of SIDS. The above findings may play a pathogenetical role in SIDS, could represent the epiphenomena of other pathological alterations causing SIDS, or could be a simple epiphenomenon of SIDS itself. The majority of findings in the carotid body, i.e., decreased volume (Naeye et al., 1976; Cole et al., 1979) and number of glomic cells (Cole et al., 1979), decrease of type I cells (Heath et al., 1990) and of dense cytoplasmic granules (Cole et al., 1979), and increase in progenitor cells (Pavai et al., 2005), indicate that the immaturity of the carotid body may play a pathogenetical role in SIDS as an underlying biological vulnerability, especially in view of the fact that carotid body function only fully develops in the postnatal period. Aorticopulmonary paraganglia hyperplasia

(Matturri et al., 1992, 1993; Ramos et al., 1998) and increase in PNEC (Cutz et al., 1988, 1996; Gillan et al., 1989; Perrin et al., 1991) may be epiphenomena of respiratory disfunctions causing SIDS. Chronic hypoxia causes hyperplasia of both aorticopulmonary paraganglia and PNEC (Dhillon et al., 1984; Pack et al., 1986; Van Lommel et al., 1999) and inflammatory or fibrotic noxae may also cause PNEC hyperplasia (Linnoila, 2006). It may also be hypothesised that in some SIDS cases hyperplasia of aorticopulmonary paraganglia and PNEC is a compensatory response to hypoplasia of carotid bodies. Further studies considering the peripheral chemoreceptors all together will be necessary to confirm this hypothesis which has previously been sustained in congenital central hypoventilation syndrome (Cutz et al., 1997). Guidelines for necropsy procedures in SIDS of the Institute of Pathology of the University of Milan, the reference centre for SIDS in Italy, provide indications for sampling of carotid body, lung and aorticopulmonary paraganglia (Matturri et al., 2005a; Institute of Pathology, 2007). These guidelines suggest using the argyrophilic Grimelius method to demonstrate neurosecretory granules in paragangliar cells. International standardised autopsy protocols in cases of sudden unexpected infant death (Krous, 1996; American Academy of Pediatrics, 2001; Royal College of Pathologists, 2004; American Academy of Pediatrics, 2006; Bajanowski et al., 2007) do not include carotid body and paraganglia among tissues to be sampled.

Most studies on the carotid body in SIDS victims focus on volume and cell number anomalies; works investigating changes in neurotransmitters (dopamine, noradrenaline) appeared only in the 1980s (Perrin et al., 1984b; Lack et al., 1986). From then on, many other neurotransmitters and neuromodulators were identified in the carotid body and postnatal changes in their content were described. Unfortunately, these new data have not yet been used to develop research programs aimed at identifying possible alterations in development of neurotransmitter/neuromodulator profiles in the carotid body.

Maternal smoking has been reported to be the external factor most significantly associated with SIDS (Tong et al., 2005). Prenatal smoke exposure reduces foetal oxygenation, through higher blood levels of carboxyhaemoglobin, increasing the infant's vulnerability to diseases, interfering with the immune system, and affecting developing organs (Lavezzi et al., 2004). Structural alterations have been reported in the cerebellum, cerebral white matter and basal ganglia of cats (Okeda et al., 1986) and in the inferior olivary nucleus (Storm et al., 1999) and arcuate nucleus (Lavezzi et al., 2004) of humans. A significant decrease in tyrosine hydroxylase immunoreactivity has also been found in the tractus solitarius nucleus, dorsal vagal motor nucleus, area postrema and hypoglossal nucleus of guinea pigs after prenatal carbon monoxide (CO) exposure (Tolcos et al., 2000). Many functional findings support the hypothesis that maternal smoking also alters the function of peripheral chemoreceptors (Gauda et al., 2004). However, morphological or neurotrasmitter alterations arising in the development of peripheral chemoreceptors have rarely been investigated. In particular, increases in tyrosine hydroxylase and dopamine ß-hydroxylase mRNA have only been found in the carotid body of newborn rats after prenatal CO exposure (Holgert et al., 1995; Gauda et al., 2001), and there are no data regarding the carotid body of SIDS cases exposed to maternal smoking. Further studies in both animals and humans should investigate the effects of prenatal CO and nicotine exposure in the carotid body and other peripheral chemoreceptors, in order to correlate these findings better with central nervous system findings, in an integrated vision of the physiopathologic mechanisms causing SIDS.

In recent years, new technologies have developed which could be applied to studying the development of peripheral chemoreceptors and new markers of SIDS. The most recent software for image analysis and morphometric techniques (Porzionato et al., 2005) also provide the necessary objectivity in analysing and comparing immunohistochemical or immunofluorescence findings. Only in recent years has the complexity of the PNEC body and processes been better evaluated by confocal microscopy, allowing 3D data to be viewed (Weichselbaum et al., 2005). In addition, the recent fresh lung slice technique and fluorescent labeled probes for neural tracing studies should better clarify NEB function in developing animals (Cutz and Jackson, 1999). The selective disruption of NEB function through recent techniques of immunotoxin targeting with antibodies against specific cell surface molecules could provide new data about the role during neonatal adaptation (Cutz and Jackson, 1999). Laser-capture microdissection has recently been applied to obtain homogeneous cell populations from endocrine and nervous structures, such as the pituitary gland (Lloyd et al., 2005), the hippocampus (Kamme et al., 2003), and the amygdala (Zirlinger and Anderson, 2003). Microarray analyses have also been performed on mRNA extracted from these cell populations. Laser-capture microdissection in conjunction with microarray analysis could allow genome-wide screening of transcripts from selective peripheral chemoreceptive cells, in comparison with other non-chemoreceptive cells and with regard to postnatal development.

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