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Preliminary Study on the Cytoarchitecture of the Human Parabrachial/Kölliker-Fuse Complex, with Reference to Sudden Infant Death Syndrome and Sudden Intrauterine Unexplained Death

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ABSTRACT

The parabrachial/Kölliker-Fuse complex has been defined, in different animal species, to lie in the dorsolateral part of the pontine tegmentum and to be subdivided into three well-defined regions: the medial parabrachial nucleus, the lateral parabrachial nucleus, and the Kölliker-Fuse nucleus. Experimental studies have shown that the parabrachial/Kölliker-Fuse complex is involved in a variety of functional activities and above all plays an important role in respiratory modulation. In human brainstem, the cytoarchitecture and physiology of this complex have not yet been fully characterized. The aim of the present study was to examine fetal and infant human brainstems in order to define the precise morphology of the three nuclei of the parabrachial/Kölliker-Fuse complex, and to determine whether this nervous center shows morphologic alterations in sudden infant death syndrome (SIDS) and in sudden intrauterine unexplained death (SIUD). In serial sections of 31 brainstems of subjects aged from 32 gestational wk to 10 months of life, we studied, by morphologic and morphometric analyses, the cytoarchitecture and the extension of the three nuclei of the parabrachial/Kölliker-Fuse complex. All the morphometric parameters were very similar in SIUD and SIDS cases to those of the respective control group, as shown by the absence of significant statistical differences between the two fetus and infant groups. We observed that the features of both the lateral and the medial parabrachial nuclei are largely consistent with those reported in experimental studies. In contrast, the Kölliker-Fuse nucleus appears to be more developed in human beings than in other animal species, showing a greater extension and a more complex structure, as well as subdivision into two subnuclei (compactus and dissipatus).

Key words: brainstem, Kölliker-Fuse, parabrachial nuclei, SIDS, SIUD, stillbirth

INTRODUCTION

The parabrachial/Kölliker-Fuse complex (PB/KF) has been defined in different animal species as a group of neurons that surround the superior cerebellar peduncle (scp) in the dorsolateral part of the pontine tegmentum. A number of experimental studies, performed by electrical and chemical stimulation of the parabrachial area, have demonstrated that the PB/KF complex is involved in a variety of functional activities and plays an important role, particularly in respiratory modulation [1–8].

In different mammalian species (rat, cat, sheep), this neuronal complex has been divided from the cytological viewpoint into three well-de-

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fined regions with distinct connections and physiological roles: the medial parabrachial nucleus (mPB), with a ventromedial localization with respect to the superior cerebellar peduncle (scp); the lateral parabrachial nucleus (lPB), located dorsally to the scp; and the Kölliker-Fuse nucleus (KF), situated ventrally to the lPB [9–13].

In human beings, the problem of tracing a morphological outline of these nuclei at histological examination and the impossibility of using experimental approaches, have made it difficult to characterize the cytoarchitecture and physiology of the human PB complex. Only a few studies have provided data regarding these structures, but the observations are imprecise and controversial [14–16].

The need to define these structures in human beings became evident during our studies on sudden infant death syndrome (SIDS) and sudden intrauterine unexplained death (SIUD).

The SIDS is defined as the sudden death of an infant under 1 year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history [17]. SIUD is defined as an unexplained late fetal death before complete expulsion of the fetus from the mother [18]. Despite a variety of proposed theories, the etiology of both SIDS and SIUD is still largely unknown.

In recent years, morphologic alterations of the arcuate nucleus (ARC), an important respiratory center of the ventral medullary surface, has been studied in these conditions [19–25]. In particular, ARC hypoplasia was first described in SIDS and considered in the light of its pathogenic implications by Filiano and Kinney in 1992 [19]. Our recent observations have identified ARC hypoplasia and agenesis in over 30% of both SIDS and SIUD victims, frequently associated with respiratory reticular formation hypoplasia and, in stillbirths, with lung hypoplasia [20–23].

From our previous studies, we concluded that it was necessary to examine in more detail the nervous structures involved in respiratory modulation, particularly the parabrachial/Kölliker-Fuse complex, that in fetal life exerts an inhibitory action on breathing which, after birth, is converted to an active respiratory-facilitating function [3, 4, 26,27, 28].

Table 1. Stillborn profiles

Case no.	Gestational age (wk)	Sex	Diagnosis of death
1	32	M	SIUD
2	32	M	Septicemia
3	33	F	Trauma during expulsion
4	34	M	Dilated cardiomyopathy
5	36	M	SIUD
6	36	F	Umbilical cord around the neck
7	36	F	SIUD
8	38	M	SIUD
9	38	M	SIUD
10	38	F	SIUD
11	39	M	SIUD
12	40	F	Umbilical cord torsion
13	40	M	SIUD

SIUD, sudden intrauterine unexplained death.

The aim of the present study was to examine serial sections of human brainstems in order to define the precise morphology, extension, and cytoarchitecture of the medial parabrachial, lateral parabrachial, and Kölliker-Fuse nuclei in man, and to determine whether these nervous centers show morphologic alterations in SIDS and SIUD. Preliminary findings have been reported in abstract form [29].

METHODS

For this study, we selected 31 brainstems obtained at autopsy from 13 stillborns (32–40 gestational wk) and 18 infants (aged 1–10 months) (Tables 1 and 2). The cause of death was diagnosed as SIUD in eight of the fetuses, whereas five (stillbirths used as control group) had died of known causes, excluding alterations of the central nervous system. At autopsy, all the stillbirths were described as well developed, with appropriate body length and weight for the gestational age, according to standard allometric growth patterns. Of the infants, 10 were SIDS victims, and in 8 (used as control group), the autopsy had established a cause of death of neither cardiorespiratory nor neuropathologic origin. Anamnesis showed that all the infants (both SIDS and controls) were born at term

Table 2. Infant profiles

Case no.	Age (months)	Sex	Diagnosis of death
1	1	M	SIDS
2	1	F	Necrotizing enterocolitis, peritonitis
3	1	M	SIDS
4	1	M	Hypertrophic cardiomyopathy
5	2	F	Pericarditis
6	2	M	SIDS
7	3	M	SIDS
8	3	F	SIDS
9	3	M	Micronodular cirrhosis
10	4	M	SIDS
11	4	F	SIDS
12	6	M	Congenital toxoplasmosis
13	6	F	Cardiac fibroma
14	7	M	SIDS
15	8	F	Acute glomerulonephritis
16	10	M	SIDS
17	11	M	SIDS
18	12	F	Extrahepatic biliary atresia

SIDS, sudden infant death syndrome.

(38–40 gestational wk), with normal values related to the percentile curves for body weight, body length, and head circumference.

After fixing in 10% buffered formalin for 3–4 days, the brainstem samples were dehydrated with ethanol at increasing concentrations and embedded in paraffin. Transverse serial 5 μm sections were made through the entire brainstem, according to the protocol routinely followed in our Institute, available on the web site: http://users.unimi.it/~pathol/sids/tecnica_e.html. Of each group of 12 sections, 3 were stained using alternately hematoxylin-eosin, Bielschowsky, and Klüver-Barrera stains, and 9 were kept and stained as deemed necessary.

The pons and mesencephalon were the particular focus of this study. The morphometric analysis was performed with an image analyzer (Image-Pro Plus; Media Cybernetics, Silver Spring, MD). For each nucleus (mPB, IPB, and KF), using serial sections stained with Klüver-Barrera through the rostrocaudal length, the neuronal cell body areas, neuronal density, transverse section areas, and volume were evaluated. Only those neurons with an obvious nucleus and nucleolus were included in the measurements. The profile area of the neuronal bodies was expressed in μm^2 and the transverse section area, after delineation of the outer boundaries, in mm^2. The neuronal density was evaluated in transverse sections as the number of neurons per mm^2. For the three-dimensional reconstruction (3-D), a computer program developed by Voxblast (Vaytek, Inc, Fairfield, IA) was used to digitize and align the anatomic boundary tracings in the serial sections (for reconstruction of their natural position in the nucleus) and to obtain volumetric measurements (in mm^3).

The morphometric data were expressed as mean values and standard deviation (mean ± SD). Statistical analysis was conducted using the SPSS method. The statistical significance of direct comparison of the means between the two fetus groups (SIUD and stillbirth controls) and two infant groups (SIDS and infant controls) was determined by one-way analysis of variance. The selected threshold level for statistical significance was $P < 0.05$.

RESULTS

The histological examination of the brainstem on serial sections has disclosed bilateral hypoplasia of the arcuate nucleus in two SIUD cases (cases 5 and 13, Table 1) and two SIDS cases (cases 6 and 16, Table 2). In a SIDS case, we have neuronal immaturity of the arcuate nucleus (case 7, Table 2). No abnormality of the arcuate nucleus was observed in the control cases.

Morphological analysis of the PB/KF complex

Comparative analysis of the serial histological sections obtained from the pons and mesencephalon of SIUD and SIDS cases with those of the two control groups (stillborns and infants, respectively), made it possible in this study to define the morphologic features of the three principal nuclei of the human PB/KF complex (IPB, mPB, and KF). This nervous structure is located in the dorsolateral region of the rostral pons. Only the KF continues along the upper side in the caudal portion of the mesencephalon. The localization of the PB/KF complex is observable in Figure 1.

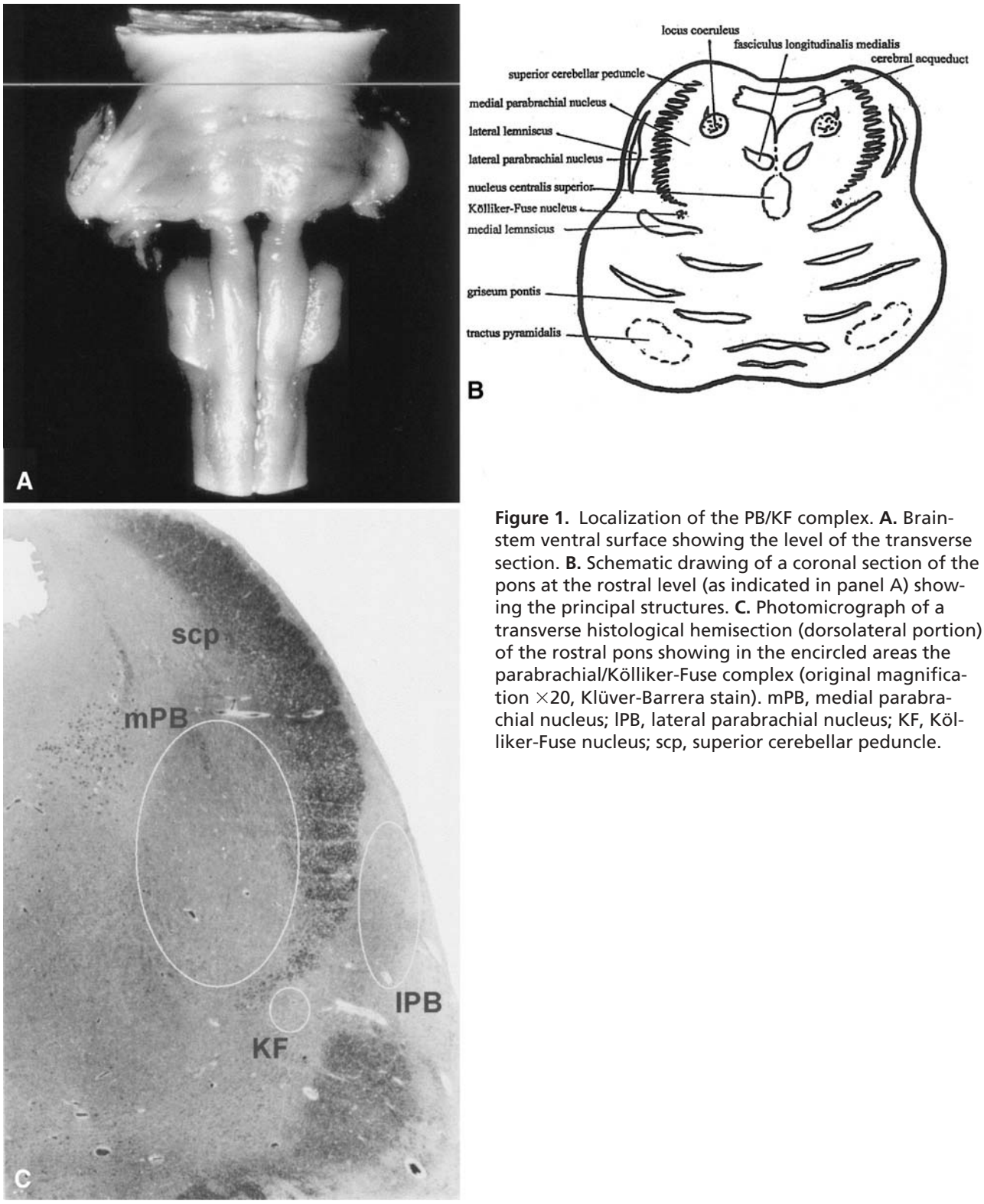

Figure 1. Localization of the PB/KF complex. **A.** Brainstem ventral surface showing the level of the transverse section. **B.** Schematic drawing of a coronal section of the pons at the rostral level (as indicated in panel A) showing the principal structures. **C.** Photomicrograph of a transverse histological hemisection (dorsolateral portion) of the rostral pons showing in the encircled areas the parabrachial/Kölliker-Fuse complex (original magnification ×20, Klüver-Barrera stain). mPB, medial parabrachial nucleus; lPB, lateral parabrachial nucleus; KF, Kölliker-Fuse nucleus; scp, superior cerebellar peduncle.

Lateral parabrachial nucleus (IPB)

In transverse sections, this nucleus is located between the lateral surface of the superior cerebellar peduncle (scp) and the lateral lemniscus. It extends rostrocaudally from the level of the pons–mesencephalon junction (cranial pole) to the level where the lateral nucleus lemniscus is clearly visible (caudal pole). The section marking the passage from the pons to the mesencephalon is recognizable because the scp forms a continuous line with their decussation.

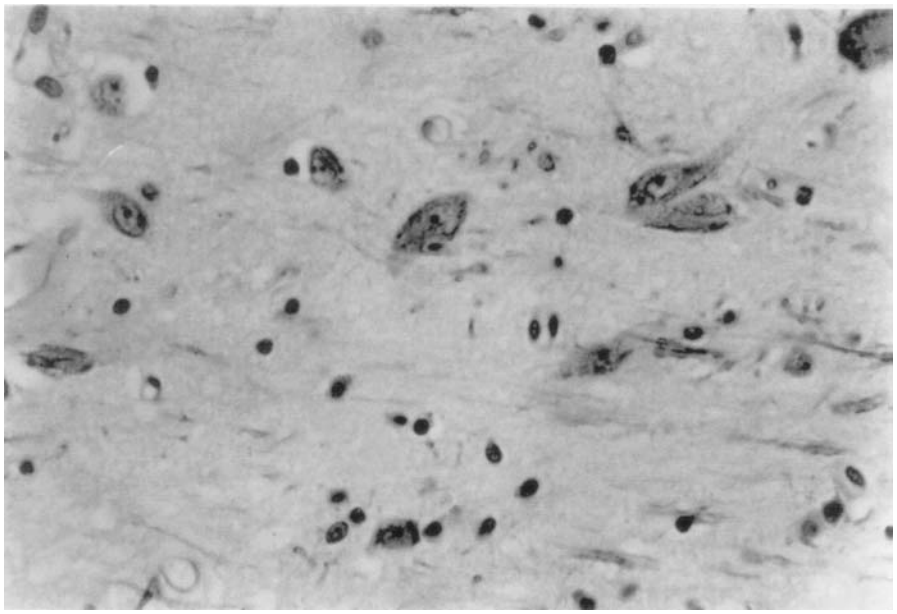

Figure 2. Neurons of the lateral parabrachial nucleus (original magnification ×400, Klüver-Barrera stain).

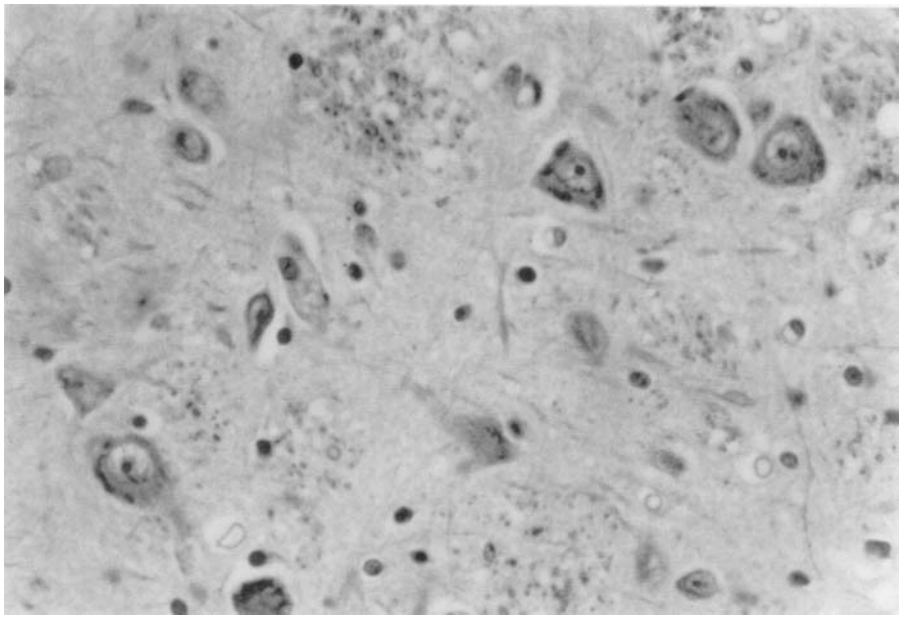

Figure 3. Neurons of the medial parabrachial nucleus (original magnification ×400, Klüver-Barrera stain).

In the more caudal sections, the IPB is reduced because the distance between the lateral lemniscus and the scp is very short. The neurons are round or tapering, with a light, often central nucleus, prominent nucleolus, and scarce cytoplasm. Many neurons are dorso-ventrally oriented, parallel to the scp axis (Fig. 2).

Medial parabrachial nucleus (mPB)

This nucleus lies medially to the scp in transverse sections, running between the motor nucleus nervi trigemini and the locus ceruleus up to the ventral termination of the scp. Longitudinally, its size does not change from the rostral pole (pons-mesencephalon junction) to the caudal pole (where the lateral nucleus lemniscus is clearly visible). It contains numerous oval and polygonal neurons, which are usually larger than the IPB neurons and have a darker and more evident cytoplasm (Fig. 3).

Kölliker-Fuse nucleus (KF)

This extends from the caudal pole of the parabrachial nuclei in the rostral pons along the whole of the lower portion of the mesencephalon, up to the level where the caudal pole of the red nucleus is visible.

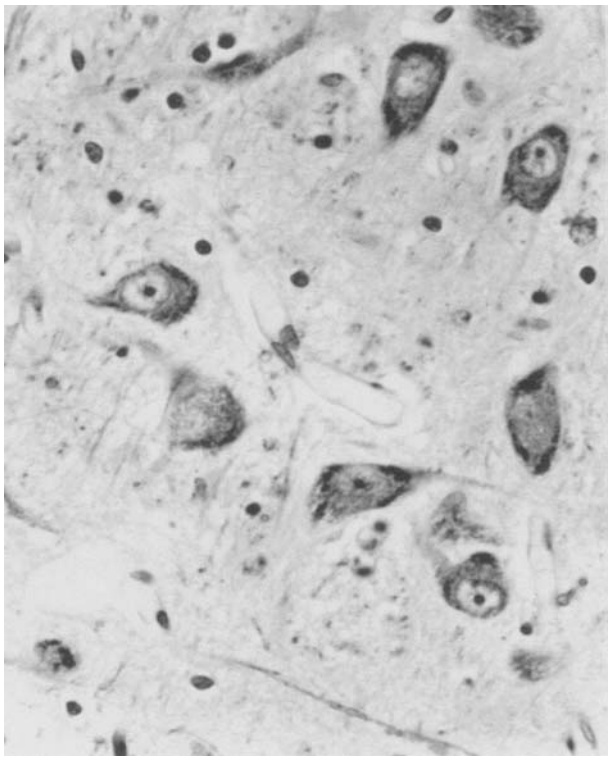

Figure 4. Neurons of the Kölliker-Fuse nucleus (original magnification ×400, Klüver-Barrera stain).

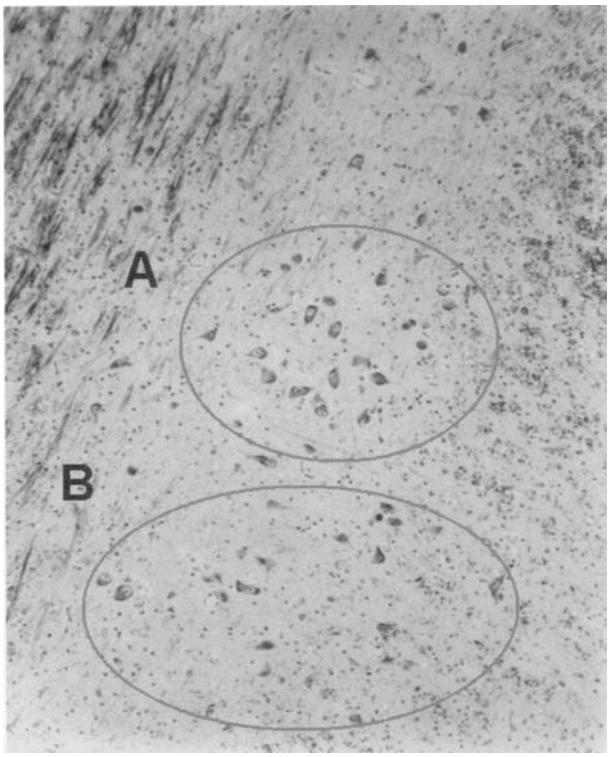

Figure 5. Configuration of the Kölliker-Fuse nucleus subdivided into two subnuclei. The encircled area **A** corresponds to the subnucleus compactus. The encircled area **B** to subnucleus dissipatus (original magnification ×100, Klüver-Barrera stain).

In transverse pontine sections, it appears as a group of large neurons, ventrally located to the IPB, between the medial limit of the scp and the medial lemniscus. The neurons, which are noticeably larger than those of the PB nuclei, have a large, distinct, eccentric nucleus with a very evident nucleolus, and abundant cytoplasm with Nissl substance located at the cell periphery (Fig. 4).

On the basis of the neuronal disposition, it is possible at all levels to define two KF subnuclei: the subnucleus compactus, made up of a cluster of a few neurons, whose outline is sometimes indistinct, and the subnucleus dissipatus, adjacent to the compactus (Fig. 5). In the more rostral sections, in the caudal mesencephalon, the KF, located between the lateral limit of the scp decussation and the medial lemniscus, shows similar cytological features and neuronal distribution.

Morphometric analysis of the PB/KF complex

Tables 3, 4, 5 6 show the morphometric evaluations related to the transverse section areas, neuronal cell body areas, neuronal density, and volume of the PB/KF complex components, respectively. All the morphometric parameters were very similar in SIUD and SIDS cases to those of the respective control group, as shown by the absence of significant statistical differences between the two fetus and infant groups. The transverse areas and volumes of the PB and KF nuclei in the stillbirth groups (SIUD and stillborn controls) were very frequently lower than those of the infants (SIDS and infant controls); instead, the neuronal cell number and cell body areas in fetuses were, on the whole, larger than the corresponding values in infants, but all these differences were not significant.

The coronal size of the IPB decreases from the cranial (total mean area in the four groups: 11.29 ± 0.20 mm^2) to the caudal pole (total mean area: 2.15 ± 0.28 mm^2). On the contrary, the transverse section areas of both mPB and KF are similar at the lower and upper extremities (mPB—total mean rostral area: 9.28 ± 0.26 mm^2, total mean caudal area: 8.55 ± 0.35 mm^2, KF—total mean rostral area: 1.75 ± 0.47 mm^2, total mean caudal area: 1.88 ± 0.25 mm^2).

Table 3. Morphometric analysis of the lPB, mPB, and KF areas[a] at the rostral and caudal level in SIUD, stillborn controls, SIDS, and infant controls*

Nucleus	Level	SIUD	Stillborn controls	SIDS	Infant controls	Total mean (± SD)
lPB	Rostral	11.0 ± 0.35	10.9 ± 0.12	12.1 ± 0.25	11.5 ± 0.17	11.29 ± 0.20
	Caudal	2.10 ± 0.31	1.85 ± 0.35	2.84 ± 0.45	2.70 ± 0.35	2.15 ± 0.28
mPB	Rostral	9.85 ± 0.16	8.78 ± 0.41	9.46 ± 0.19	9.55 ± 0.35	9.28 ± 0.26
	Caudal	8.13 ± 0.43	9.11 ± 0.20	8.63 ± 0.25	7.91 ± 0.16	8.55 ± 0.35
KF	Rostral	1.22 ± 0.40	1.92 ± 0.28	2.13 ± 0.36	1.95 ± 0.80	1.75 ± 0.47
	Caudal	2.13 ± 0.44	1.89 ± 0.20	1.70 ± 0.25	1.91 ± 0.15	1.88 ± 0.25

lPB, lateral parabrachial nucleus; mPB, medial parabrachial nucleus; KF, Kölliker-Fuse nucleus.
[a]Expressed in mm^2 as mean ± SD.
*Level of significance $P > 0.05$.

Table 4. Morphometric analysis of the mean (± SD) neuronal cell body areas[a] in serial transverse sections of the lPB, mPB, and KF in the two groups of fetuses and two groups of infants*

Nucleus	SIUD	Stillborn controls	SIDS	Infant controls	Total mean (± SD)
lPB	280 ± 0.70	275 ± 0.41	268 ± 0.18	259 ± 0.20	268.70 ± 0.36
mPB	340 ± 0.40	319 ± 0.16	310 ± 0.25	288 ± 0.32	310.58 ± 0.28
KF	890 ± 0.12	898 ± 0.64	855 ± 0.15	868 ± 0.50	878 ± 0.40

[a]Expressed in μm^2 ± SD.
*Level of significance $P > 0.05$.

Table 5. Morphometric analysis of the mean (± SD) neuronal density[a] in serial transverse sections of the lPB, mPB, and KF in the two groups of fetuses and two groups of infants*

Nucleus	SIUD	Stillborn controls	SIDS	Infant controls	Total mean (± SD)
lPB	34 ± 12	35 ± 5	29 ± 8	31 ± 3	31 ± 11
mPB	44 ± 14	42 ± 8	38 ± 10	37 ± 15	39 ± 12
KF	33 ± 6	34 ± 8	28 ± 15	28 ± 11	33 ± 10

[a]Neuron-number/mm^2.
*Level of significance $P > 0.05$.

Comparing the body section areas of the three PB/KF nuclei, it is evident that the mPB neurons are larger than the IPB neurons (total mean values: μm^2 310.58 ± 0.28 and 268.70 ± 0.36, respectively) and that the KF neuron areas are significantly larger, being more than twice as big as the PB neurons (mean value: μm^2 878 ± 0.40).

DISCUSSION

It has often been observed in experimental studies that the PB and KF nuclei play an essential role in respiratory modulation. Moreover, the KF also has an important function during intrauterine life, inhibiting the response of central and peripheral chemoreceptors (which are already fully formed and potentially functional) and therefore any respiratory reflex [1–8]. From birth, the KF abruptly reduces its inhibitory effects and becomes active as a respiratory center able to coordinate the pulmonary motor responses to hematic oscillations of pO_2, pCO_2, and pH [3, 4, 31]. Detailed studies on the parabrachial complex in the rat [31–33] based

Table 6. Morphometric analysis of the volume[a] of the lPB, mPB, and KF in the two groups of fetuses and two groups of infants*

Nucleus	SIUD	Stillborn controls	SIDS	Infant controls	Total mean (± SD)
lPB	5.51 ± 0.50	5.35 ± 0.34	6.71 ± 0.53	6.16 ± 0.39	5.98 ± 0.44
mPB	8.52 ± 0.43	8.47 ± 0.46	8.62 ± 0.34	8.44 ± 0.38	8.35 ± 0.40
KF	2.04 ± 0.69	2.51 ± 0.51	2.17 ± 0.42	2.55 ± 0.15	2.37 ± 0.55

[a]Expressed in mm^3 ± SD.
*Level of significance $P > 0.05$.

on the anterograde and retrograde transport of specific agglutinins, have shown that the PB and KF nuclei can divide into subnuclei with distinct connections and physiological roles. Only limited tracts of the PB-KF complex appear to be involved in the respiratory function and present reciprocal afferent and efferent connections with the medullary respiratory centers, in particular with the nucleus tractus solitarii (medio-caudal portion), with the reticular respiratory formations and the nucleus ambiguus. [34,35] The rostral tract of the KF and the lateral part of the mPB seem to inhibit the neurons of the medulla oblongata, which are responsible for inspiration, and at the same time to stimulate those responsible for expiration. The ventro-lateral region of the IPB, in the rostral and intermediate tracts, seems to have the opposite effect, enhancing inspiratory activity. This subnucleus of the IPB is thought to be the relay center for mediating the excitatory signals coming from the central and peripheral chemoreceptors [35,36].

Experimental studies have clearly defined not only the physiological roles but also the cytoarchitectural organization of the PB/KF complex. However, precise morphologic data regarding this structure in man are still lacking [14–16].

In the present work, based on examination of human fetal and infant brainstems, we define the structure and extension of the three nuclei of the PB/KF complex. We limited the study to subjects of ages ranging from the 32nd wk of gestation to 7 months, in whom the process of myelinization of the nerve fibers is still incomplete,[37] so it is easier to examine the PB structures. Instead, in adults, the relative density of myelinized fibers of the scp and lateral lemniscus often covers the cells, making it difficult to recognize these structures.

The sample included prevalently cases of SIDS and SIUD, as the aim was also to determine whether these syndromes, whose etiology is still unknown, show structural alterations in the pontine respiratory centers. However, the results demonstrated neither morphologic nor morphometric differences of the PB/KF complex as compared with the control cases, also in cases presenting arcuate nucleus hypoplasia compared with the controls.

Our observations of the morphology and extension of the two parabrachial nuclei, medial and lateral, are largely consistent, even if their boundaries are not so clearly defined, with those of other experimental studies. In fact, reports in other species refer that the PB nuclei surround the scp in the dorsolateral pons and extend longitudinally from the level of the pons–mesencephalon junction to the caudal pole, where the lateral nucleus lemniscus is still visible. Instead, we found some morphologic differences in the KF between man and experimental animals, namely: (1) in man, it has a lesser degree of definition and circumscription; (2) as appreciated in transverse sections, it is made up of an area of clustered neurons (the subnucleus compactus) and an adjacent area with scattered neurons (the subnucleus dissipatus); (3) it is not restricted to the cranial portion of the pons, but is also detectable in the caudal tract of the mesencephalon.

On the basis of these observations, it can be concluded that the KF appears to be more developed in human beings than in other species, and that it shows a more extended and complex structure, with morphological connections to the mesencephalon.

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REFERENCE

1. Chamberlin NL, Saper CB. Topographic organization of respiratory responses to glutamate microstimulation of the parabrachial nucleus in the rat. J Neurosci 1994;4:6500–6510.
2. Cohen M. Switching of the respiratory phases and evoked phrenic responses produced by rostral pontine electrical stimulation. J Physiol (Lond) 1971;217:133–158.
3. Cohen M. Neurogenesis of respiratory rhythm in the mammal. Physiol Rev 1979;59:91–104.
4. Feldman JL. Neurophysiology of breathing in mammals In: Bloom FE, (eds.). Handbook of Physiology, Section 1. The Nervous System. vol. IV: Intrinsic Regulatory System of the Brain. Bethesda, MD: American Physiological Society, 1986;463–524.
5. Hirano T, Simbulan D, Kumayawa T. Effects of kainic acid in the parabrachial region for ongoing respiratory activity and reflexive respiratory suppression. Brain Res 1994;665:54–62.
6. Miura M, Takayama K. Circulatory and respiratory responses to glutamate stimulation of the lateral parabrachial nucleus of the cat. J Auton Nerv Syst 1991;32:121–134.
7. Takayama K, Miura M. Respiratory responses to microinjection of excitatory amino acid agonist in ventrolateral regions of the lateral parabrachial nucleus in the cat. Brain Res 1993;604:217–223.
8. Younes M, Baker J, Remmers JE. Temporal changes in effectiveness of an inspiratory inhibitory electrical pontine stimulus. J Appl Physiol 1987;62:1502–1512.
9. Berman AL. The Brainstem of the Cat: A Cytoarchitectonic Atlas with Stereotaxic Coordinates. Madison, WI: University of Wisconsin Press, 1968.
10. Paxinos G, Watson C. The Rat Brain in Stereotaxic Coordinates. London: Academic Press/Harcourt Brace Jovanovich, 1986.
11. Saper CB. Central autonomic system In: Paxinos G, (eds.). The Rat Nervous System, 2nd ed. San Diego: Academic Press, 1995;107–135.
12. Taber E. The cytoarchitecture of the brain stem of the cat. J Comp Neurol 1961;116:37–70.
13. Yoshikawa T. The brain of the sheep. In: Atlas of the Brains of Domestic Animals. Tokyo: University of Tokyo Press, 1968.
14. Block CH, Estes M. The cytoarchitectural organization of the human parabrachial nuclear complex. Brain Res Bull 1990;24:617–626.
15. Gioia M, Rodella L, Petruccioli MG, Bianchi R. The cytoarchitecture of the adult human parabrachial nucleus: a Nissl and Golgi study. Arch Histol Cytol 2000;63:411–424.
16. Olszewski J, Baxter D. Cytoarchitecture of the Human Brain Stem. Basel, Switzerland: Karger, 1982.
17. Willinger M, James S, Catz C. Defining the SIDS: deliberations of an expert panel convened by the National Institute of Child Health and Human Development. Pediatr Pathol 1991;11:127–132.
18. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk factors for sudden intrauterine unexplained death: epidemiologic characteristics of singleton cases in Oslo, Norway, 1986–1995. Am J Obstet Gynecol 2001;184:694–702.
19. Filiano JJ, Kinney HC. Arcuate nucleus hypoplasia in the sudden infant death syndrome. J Neuropathol Exp Neurol 1992;51:394–403.
20. Matturri L, Ottaviani G, Alfonsi G, Crippa M, Rossi L, Lavezzi AM. Study of the brainstem, particularly the arcuate nucleus, in sudden infant death syndrome (SIDS) and sudden intrauterine unexplained death (SIUD). Am J Forensic Med Pathol 2004 (in press).
21. Matturri L, Biondo B, Suàrez-Mier MP, Rossi L. Brain stem lesions in the sudden infant death syndrome: variability in the hypoplasia of the arcuate nucleus. Acta Neuropathol 2002;194:12–20.
22. Matturri L, Minoli I, Lavezzi AM, Cappellini A, Ramos S, Rossi L. Hypoplasia of medullary arcuate nucleus in unexpected late fetal death (stillborn infants): a pathologic study. Pediatrics 2002;109:E43.
23. Matturri L, Lavezzi AM, Minoli I, et al. Association between pulmonary hypoplasia and hypoplasia of arcuate nucleus in stillbirth. J Perinatol 2003;23:328–332.
24. Grafe MR, Kinney HC. Neuropathology associated with stillbirth. Semin Perinatol 2002;26:83–88.
25. Nachmanoff DB, Panigray A, Filiano JJ, et al. Brainstem 3H-nicotine receptor binding in the sudden infant death syndrome. J Neuropathol Exp Neurol 1998;57:1018–1025.
26. Euler C. Brainstem mechanisms for generation and control of breathing pattern In: Cherniack NS, Waddicombe JG, (eds.). Handbook of Physiology, Section 3. Respiration. Vol. II: Control of Breathing. Bethesda, MD: American Physiological Society, 1986;1–67.
27. Orem J, Trotter RH. Post-inspiratory neuronal activities during behavioral control, sleep and wakefulness. J Appl Physiol 1992;72:761–769.
28. Lavezzi AM, Ottaviani G, Rossi L, Matturri L. Cytoarchitectural organization of the parabrachial/Kölliker-Fuse complex in man. Brain Dev 2004 (in press).
29. Lavezzi AM, Ballabio G, Ottaviani G, Matturri L, Rossi L. Study of the cytoarchitecture of the parabrachial/Kölliker-Fuse complex in SIDS and fetal late stillbirth (Abstract). Proceedings of the 7th SIDS International Conference, Florence, Italy. 2002;132.
30. Blanco CE, Dawes GS, Hanson MA, McCooke HB. The response to hypoxia of arterial chemoreceptors in fetal sheep and newborn lambs. J Physiol 1984;351:25–37.
31. Fulwiler CF, Saper CB. Subnuclear organization of the efferent connections of the parabrachial nucleus in the rat. Brain Res Rev 1984;7:229–259.
32. Granata A. Ascending and descending convergent inputs to neurons in the nucleus parabrachialis of the rat: an intercellular study. Brain Res 1993;600:315–321.
33. Herbert H, Moga MM, Saper CB. Connections of the parabrachial nucleus with the nucleus of the solitary tract and the medullary reticular formation in the rat. J Comp Neurol 1990;293:540–580.
34. Segers LS, Shannon R, Lindsey BG. Interactions between rostral pontine and ventral medullary respiratory neurons. J Neurophysiol 1985;54:318–334.
35. Schmid K, Bohmer G, Fallert M. Medullary respiratory-related neurons with axonal connections to rostral pons and their function in termination of inspiration. Pflugers Arch 1985;403:58–65.
36. Holmes HR, Herbert H, Saper CB. Parabrachial subnuclei in respiratory control. Soc Neurosci 1987;13:1586 (abstract).
37. Barness EG. Respiratory system In: Barness EG, (eds.). Potter's Pathology of the Fetus and Infant. St. Louis: Mosby, 1997;712–773.