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Invited Review

Distribution of central catecholaminergic neurons: a comparison between ungulates, humans and other species

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Summary. In ungulates and primates, the distribution of central catecholaminergic neurons identified using antibodies raised against catecholamine synthesizing enzymes and catecholamines themselves, shows many differences if compared to rats. Catecholaminergic neurons are more loosely clustered in ungulates and primates than in rat. In the medulla oblongata, the density of noradrenergic/adrenergic neurons is lower in ungulates than in other species and, particularly in sheep, the adrenergic group C1 is not observed. The noradrenergic neurons of the locus coeruleus are present in a larger area in ungulates than in rodents. In the hypothalamus, the density of dopamine neurons is lower in ungulates and primates than in rodents. In the rostral hypothalamus of ungulates, the dorsal part of the group A14 is missing, and these species present only the ventral part of the group A15. In primates the group A15 extends into the supraoptic and paraventricular nuclei which have large tyrosine hydroxylase-immunoreactive (TH-IR) neurons not observed in other species. In addition, in all studied species, not all cells expressing catecholamine synthesizing enzymes also express catecholamines, as found in some TH-IR neurons in the arcuate nucleus, thereby demonstrating the necessity of using different markers to ascertain the true catecholaminergic nature of labeled neurons. These anatomical differences between species show the difficulty in extrapolating the distribution of catecholamine neurons from one species to another and may be related to adaptative physiological differences between mammals.

Key words: Catecholamine, Central nervous system, Domestic mammals, Primates

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Introduction

The monoaminergic neurons have been first described in rodents by the histofluorescence method (Dahlström and Fuxe, 1964, 1965; Fuxe, 1965a,b) and numerous studies have been conducted in these animals. Investigations in primates, particularly in humans, started a few years later (Nobin and Björklund, 1973), mainly for applied medical research consideration. Only little attention has been devoted to the other species like farm animals. Comparison of distribution of monoamine-containing neurons between rats and humans indicates noteworthy species differences in the fine organization of these neurons. Therefore, it is hazardous to use information from one species to another, and an acute knowledge of these neuronal systems seems indispensable for each studied species.

Monoamines are critically involved in many neuroendocrine regulations (reproduction, growth, lactation, stress...) and autonomic functions, as largely described in rodents and sometimes in humans (Weiner and Ganong, 1978; Tuomisto and Männistö, 1985; Loewy and Spier, 1990). These neuroendocrine and autonomic regulations are now studied in other species such as pigs and ruminants which constitute an alternative experimental model to rodents. In addition, from an agricultural perspective, there is increasing interest to understand regulations that affect numerous functions and behavioral patterns in domestic animals.

In sheep, a seasonal breeder, dopamine and noradrenaline are involved in the seasonal control of LH secretion (Thiéry et al., 1995). In all farm animals as well as in rodents, catecholamines are involved in the physiological response to stress which could decrease animal production (Dantzer et al., 1983; Signoret, 1983; Dantzer, 1986). In pigs and ruminants autonomic innervation of the digestive tract plays an important role in the control of digestion.

The pig is used as an experimental model for human cardiovascular, respiratory and gastrointestinal

physiology (Tumbleson, 1986). In the field of intracerebral grafting, neurons of the pig ventral mesencephalon have been used to correct motor asymmetry in the rat model of Parkinson disease (Huffaker et al., 1989). In addition, domestic animals could present neuronal disorders suitable for studying neurodegenerative processes: sheep scrapy and bovine spongiform encephalopathy could constitute an interesting model of Creutzfeldt-Jakob disease. In these species, an acute knowledge of catecholaminergic neurons is essential to understand these regulations.

In all neuroanatomical studies and particularly in those concerning catecholamine-containing neurons, the delay between death and tissue fixation is critical: the shorter the postmortem delay, the better the preservation of the structures. Under slaughter conditions, especially, it is sometimes difficult to perform brain perfusions in large animals (cow or pig). In such conditions quality of the tissue is very low and the demonstration of catecholamine molecules is difficult either using formaldehyde-induced fluorescence or immunohistochemistry with antibodies raised against dopamine or noradrenaline. However, using immunohistochemistry of catecholamine-synthesizing enzymes, it becomes possible to study their distribution in brain tissues of several species of farm animals (Tillet, 1988; Tillet and Thibault, 1989; Ostergaard et al., 1992; Ruggiero et al., 1992; Kitahama et al., 1994; Leshin et al., 1995a,b, 1996). Antibodies raised against the enzyme of catecholamine synthesis (phenylethanolamine-N-methyl transferase, PNMT; dopamine-beta-hydroxylase, DBH; aromatic L-amino-acid decarboxylase, AADC or tyrosine hydroxylase, TH) were used to detect adrenergic, noradrenergic and dopaminergic neurons, respectively. In this short review, we present the main characteristics of the distribution of catecholaminergic neurons in large breeding animals compared to their organization in human, monkey, cat and rat.

As a common frame, we used the nomenclature of catecholamine neuronal group previously determined in rats by Hökfelt et al. (1984b), although many differences exist between the brains of rats, ungulates and primates. Catecholamine neuronal structures were described from caudal to rostral levels.

1. Medulla oblongata

Catecholaminergic neurons in the medulla oblongata are believed to play an important role in autonomic regulation, such as cardiovascular, respiratory and general visceral controls (Törk et al., 1990). Morphologically, they were first demonstrated by Dahlström and Fuxe (1964) to display green histofluorescence in the rat, and to be distributed through the entire extent of the medulla. These authors classified them into two groups, A1 and A2; A1 cells were clustered in the ventrolateral medulla (VLM) and A2 cells were concentrated in the dorsomedial medulla. The application of immunohistochemistry for catecholamine synthesizing enzymes made it possible to divide them into 2 subgroups: A1/A2 noradrenergic and C1/C2 adrenergic cell groups. The former is composed of caudally situated TH- and DBH-ir cells and is considered to be noradrenergic, and the latter consists of rostrally situated ones which are also immunoreactive for PNMT and considered to be adrenergic (Hökfelt et al., 1974, 1984a; Howe et al., 1980; Kalia et al., 1985a,b).

1.1. Caudal medulla oblongata

1.1.1.A1 cell group

In the rat, the majority of TH-ir and DBH-ir neurons are restricted to a small area of the VLM caudal to the area postrema. They extend up to the spinomedullary junction. These cells, which do not show PNMT-immunoreactivity, are thus believed to be noradrenergic. We have noted the similar distribution patterns of such cells in the cat and primate homologous region. However, such presumptive noradrenergic neurons are less in number in the ungulate VLM, and are not detectable in the sheep spino-medullary junction.

1.1.2. A2 cell group

In the rat and cat, TH- and DBH-ir neurons, which are not immunoreactive for PNMT, are concentrated in the commissural subnucleus (of the nucleus of the solitary tract (NTS)) and extend up to the spinomedullary junction, where they are present mainly around the central canal. In the human commissural region, they are scattered through the nucleus. In ungulates, at least in sheep and cattle, they are far lower in number in the dorsal vagal complex and do not extend more caudally.

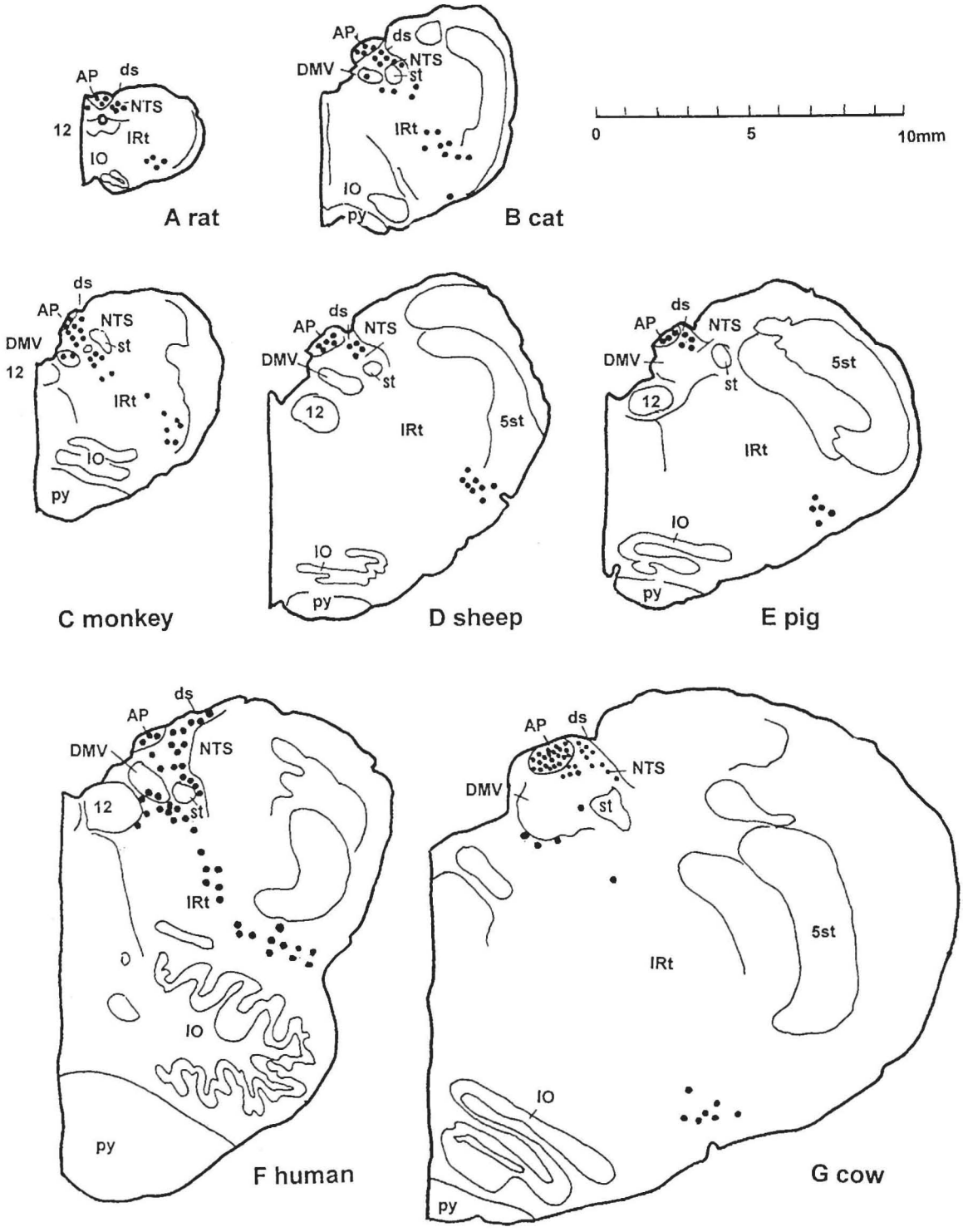
1.2. Rostral medulla oblongata

1.2.1. C1 and rostral A1 cell groups

In the rat (Fig. 1A), rostrally situated TH/DBH-ir cells which also contain PNMT, form a compact aggregate mainly in the lateral paragigantocellular nucleus (PGCL) (Hökfelt et al., 1984a), and some extend dorsally in the reticular formation. Such cells are defined as the C1 group as mentioned above.

In other species, such as carnivores, ungulates and primates, we found several important species differences in cell organization when compared with rodents, as we describe below.

In the cat brain (Fig. 1B), TH- and DBH-ir cells are concentrated in the VLM dorsal to the lateral reticular nucleus, but many are dispersed more dorsally in the reticular formation (equivalent to the rat intermediate reticular nucleus according to Paxinos and Watson, 1986) and virtually all the stained cells show PNMT-immunoreactivity and are considered to be adrenergic



Figs. 1- 3. Schematic drawing of frontal sections through the brain of rat **(A)**, cat **(B)**, monkey **(C)**, sheep **(D)**, pig **(E)**, human **(F)** and cow **(G)**. Black dots have been placed were TH-ir neurons are observed. Abbreviations used in the figures (According Paxinos and Watson, 1986). AP: area postrema; DMV: dorsomedial nucleus of the vagus; ds: nucleus of the tractus solitarius, dorsal part; fx: fornix; IO: inferior olive; IRT: intermediate reticular nucleus; LC: locus coeruleus; LSC: locus subcoeruleus; NTS: nucleus of the tractus solitarius; ot: optic tract; PEH: periventricular hypothalamic nucleus; PnC: pontine reticular nucleus, caudal part; PVH: paraventricular hypothalamic nucleus; py: pyramidal tract; scp: superior cerebellar peduncles (brachium conjonctivum); SON: supraoptic nucleus; st: solitary tract; VMN: hypothalamic ventromedial nucleus; V3: third ventricle; 12: hypoglossal nucleus; 5st: mesencephalic tract of the trigeminal nerve nucleus.

Fig. 1. Sections through the medulla oblongata, at the level of the area postrema.

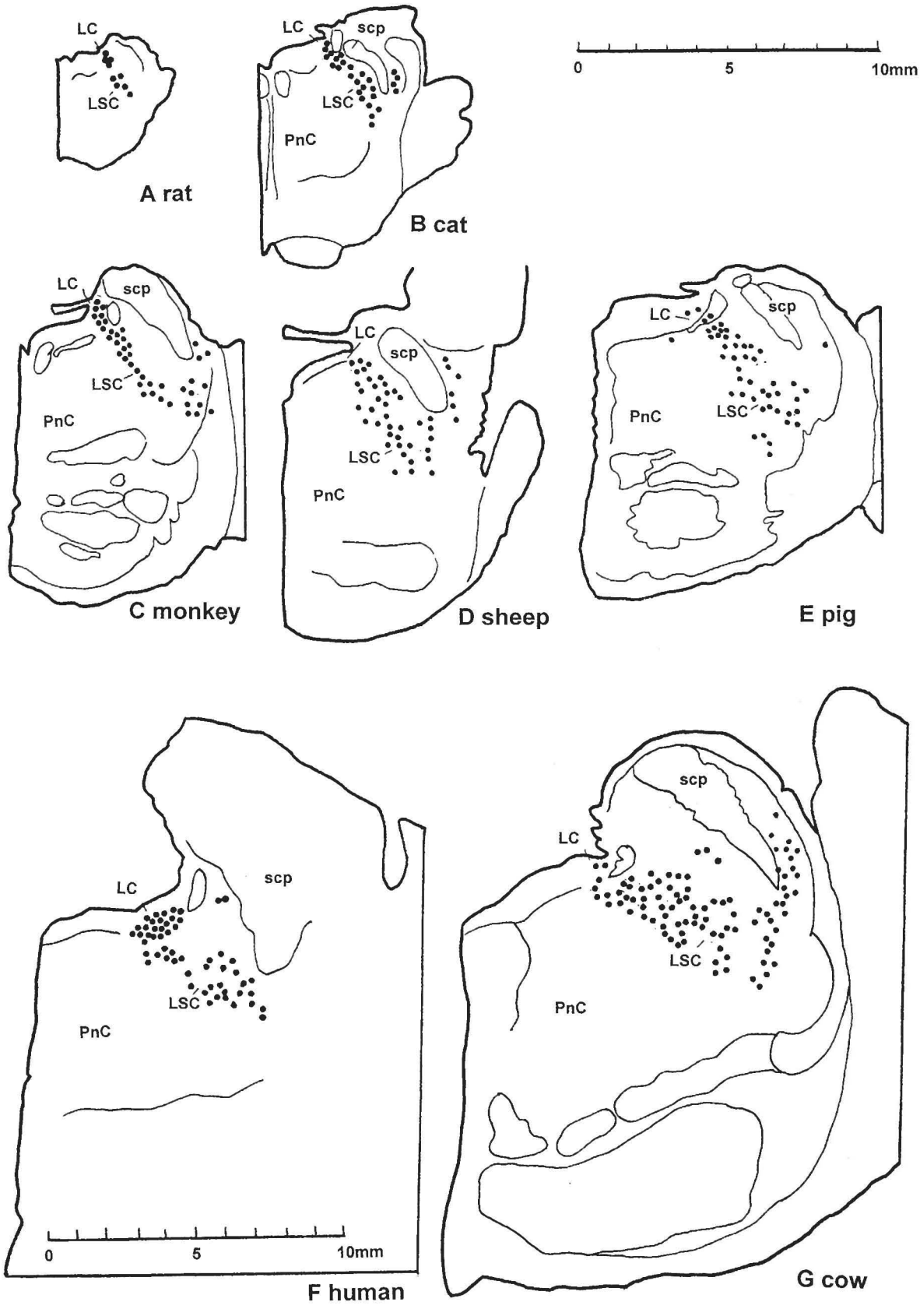


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Fig. 2. Sections through the pontine area, at the level of the locus coeruleus.

(Kitahama et al., 1986; Reiner and Vincent, 1986; Ruggiero et al., 1986).

In the human brain (Fig. 1F), DBH-ir neuronal cell bodies form a band to connect the dorsomedial and ventrolateral parts through the intermediate medullary reticular formation, in the ventral part of which some are aggregated but not found in the PGCL. PNMT-ir cells are fewer in number than TH/DBH-ir cells. Therefore, it is considered that noradrenergic and adrenergic neurons are intermingled in this region (Kitahama et al., 1985,

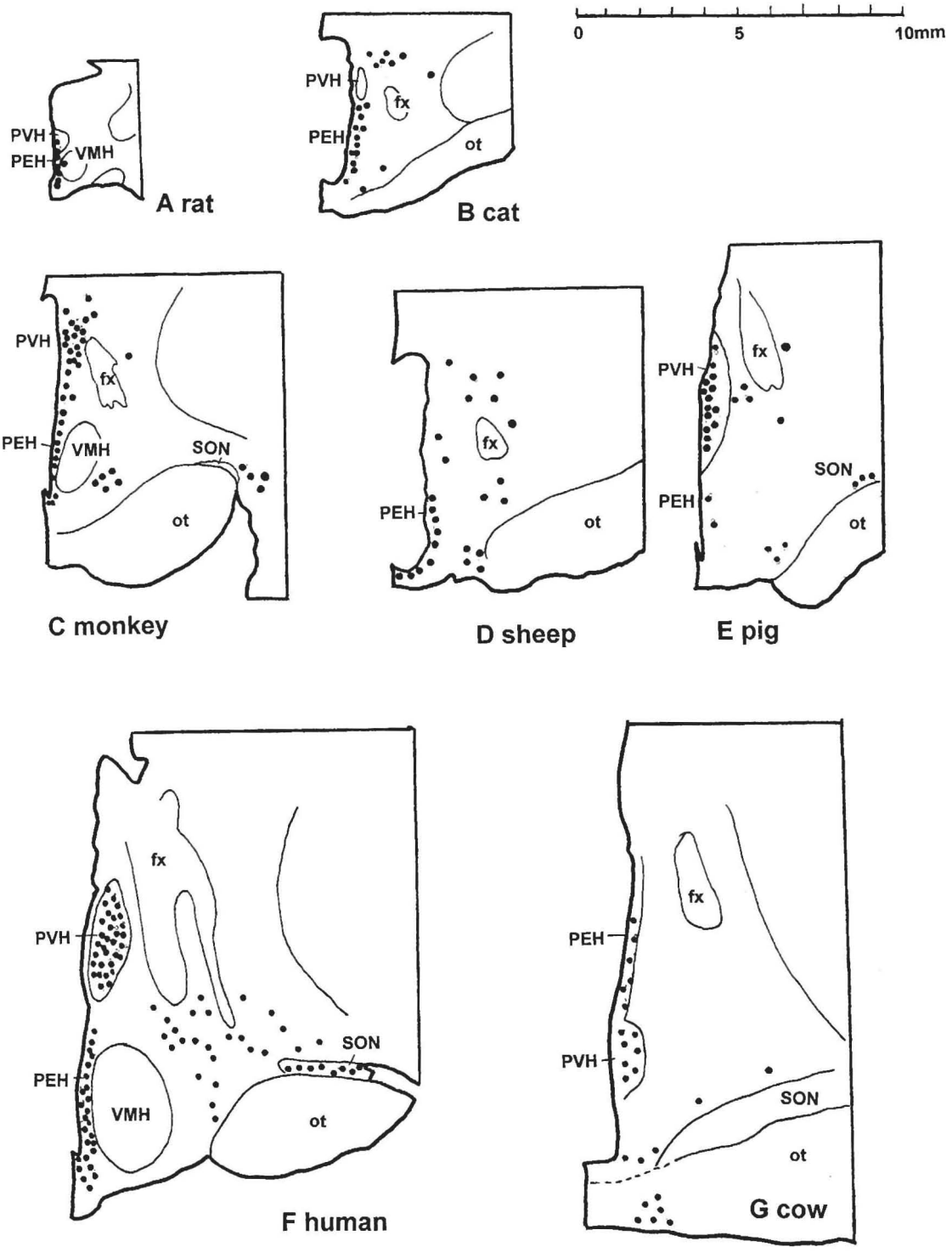

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Fig. 3. Sections through the hypothalamus at the level of the paraventricular nucleus.

1996).

In ungulates, their equivalent TH-/DBH-ir cells are, in general, restricted to the ventrolateral quadrant of the medulla, especially in the reticular formation ventrolateral to the nucleus ambiguus (Fig. 1D, E, G). PNMT-ir cell bodies are smaller in number than those staining for TH/DBH throughout mid-medullary levels of the VLM of cattle (Fig. 4). According to Ruggiero et al. (1992), TH-/DBH-ir neurons outnumber and are more broadly distributed than those stained for PNMT throughout the caudal and mid-medullary levels of the VLM, especially at levels extending caudally through the area postrema and posteriorly to the obex. In sheep, no PNMT-ir cell bodies are found in the VLM (Tillet, 1988) (Fig. 4 C,D).

It should be noted that in the human rostral VLM, TH-ir neurons outnumber those showing DBH and PNMT immunoreactivity (Kitahama et al., 1996) as reported in the pig (Ruggiero et al., 1992). At present, it is not known if they contain L-DOPA, a direct product of TH.

1.2.2. C2 and rostral A2 cell groups

This group is mainly located in the dorsal vagal complex of the rostral dorsomedial medulla.

In the rat (Fig. 1A), the C2 cell group is localized in the medial portion of the NTS (mNTS), and contains TH, DBH and PNMT. A compact cell group, being formed by many small neurons, is found in the dorsal portion of the NTS (dorsal strip) at the level of the area postrema. Although some TH-ir cells are distinguished in the dorsal motor nucleus of the vagus (DMV), no PNMT-ir cells are found in this nucleus.

In the cat (Fig. 1B), at the level of the area postrema, TH-ir cells are seen mainly in the ventral and dorsal subnuclei of the NTS, where PNMT-ir cells are fewer in number. Some small TH-ir cells are seen in the dorsal strip.

The human NTS (Fig. 1F) contains many small and a few medium-sized triangular fusiform DBH/TH neuronal cell bodies. The population increases rostrally and is distributed in the dorsal two-thirds of the NTS,

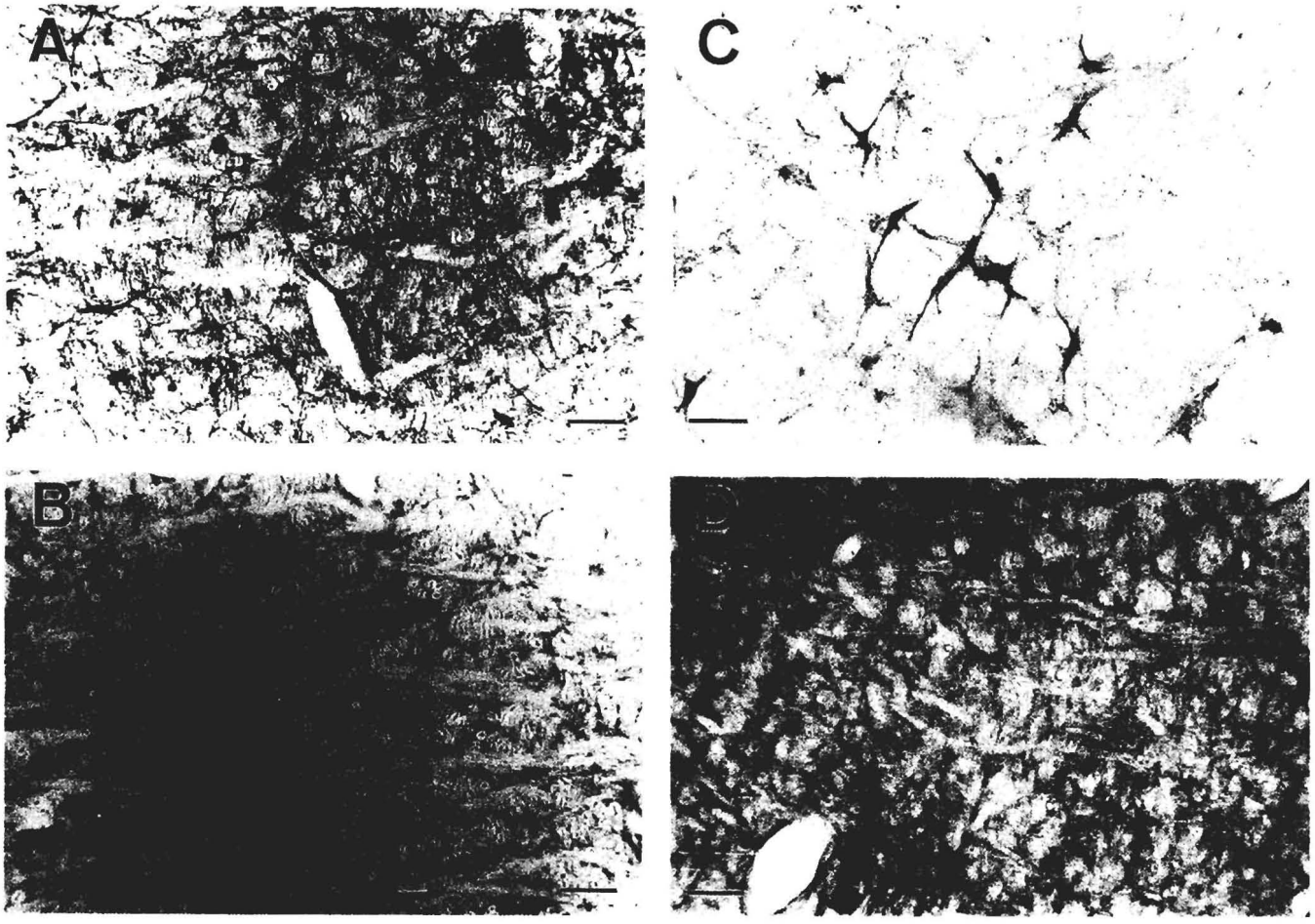

Fig. 4. Frontal sections through the ventrolateral medulla oblongata of the cow **(A, B)** and sheep **(C, D)**. A. TH immunoreactive neurons of the group A1/C1. C. DBH immunoreactivity found in the same area of the sheep. B and D are successive sections to A and C, labeled with a serum anti PNMT. Note the absence of PNMT immunoreactive neurons in the area corresponding to the group C1 of the sheep. Scale bars: 100 μm.

but shuns the subnucleus gelatinosus within which bipolar cell bodies are immunoreactive for TH only. This subnucleus contains packed PNMT-ir cells (Kitahama et al., 1985, 1988). TH-only cells are also seen in the dorsomedial portion of the NTS and DMV. PNMT-ir cells are far fewer in number in this region except in the subnucleus gelatinosus.

In the pig, as shown in Fig. 1E, PNMT-ir neurons are concentrated in the NTS throughout the medulla. As observed in the human (Kitahama et al., 1985, 1988), a dorsal group of small PNMT-ir neurons forms a dense circular condensation at the dorsolateral edge of the nucleus subpostrema (Ruggiero et al., 1992). In the neonatal swine, large numbers of TH- and DBH-ir neurons in the NTS are skewed ventrally or laterally to the C2 area where PNMT-ir cells are concentrated.

In cattle (Fig. 1G), some TH- and DBH-ir cells are dispersed in the NTS medially to the solitary tract and dorsally to the DMV. Many of them are seen in the subpostrema region subjacent to the area postrema, in which a large number of TH-ir cells are packed. In these areas rare PNMT-ir cell bodies are detectable, with the exception of some labeled ones in the dorsal strip, in which a few TH-ir ones are present (Fig. 5).

In sheep (Fig. 1D), rostrally located cells are TH-ir and DBH-ir, and packed in the dorsomedial portion of the NTS, in which several PNMT-ir cells are recognized (Fig. 6).

It should be underlined that in the rostral medulla oblongata, PNMT-ir neurons are much smaller in number than DBH-ir ones in the human and cow; adrenergic cells are intermingled with noradrenergic ones in the rostral medulla of these species. Furthermore, no PNMT-ir cells are found in the C1-homologous region of the sheep (Tillet, 1988). This evidence indicates that C1 adrenergic cells are not present in the sheep brain. Therefore, it does not sound appropriate to define all the TH/DBH-ir cells in this region as C1 adrenergic cells at least in the human and ungulates. For this reason, we temporarily call, at the present, these

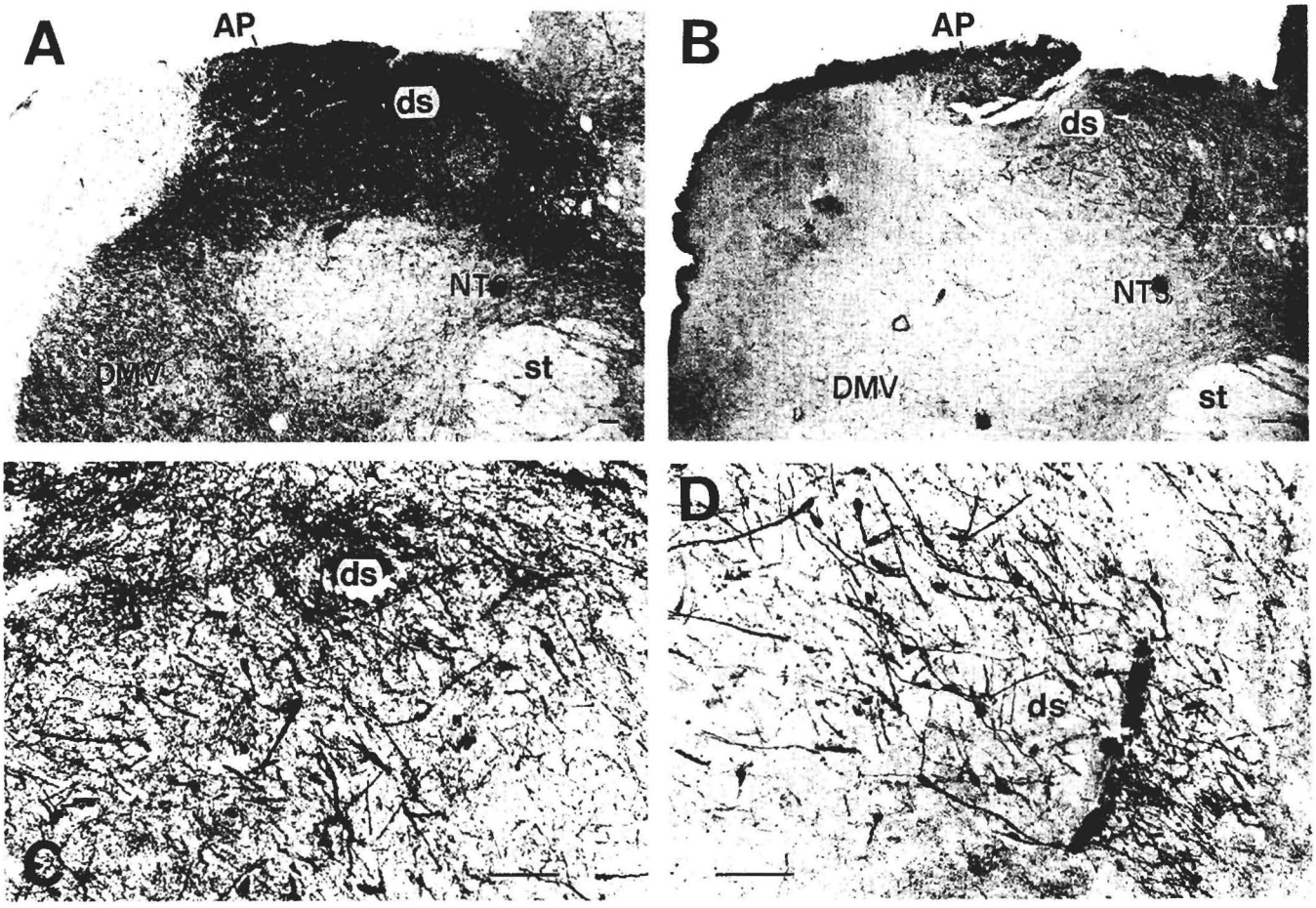

Fig. 5. Frontal sections through the dorsomedial area of the medulla oblongata, at the level of the area postrema of the cow. **A.** TH immunoreactive neurons. **B.** represents PNMT immunostaining obtained on the successive section. **C and D** are a higher magnification of A and B, respectively. AP: area postrema; DMV: dorsomedial nucleus of the vagus; ds: nucleus of the tractus solitarius, dorsal part; NTS: nucleus of the tractus solitarius; st: solitary tract. Scale bars: 100 μm.

subgroups rostral A1/A2 cell groups.

1.3. C3 cell group

This group, composed of dispersed TH- and PNMT-ir neurons seen in the rat dorsal midline of the rostral medulla, is also recognized in the human and neonatal swine homologous region (Ruggiero et al., 1992; Gai et al., 1993). However, it is not detectable in cat and sheep. In the rat, immunoreactivity for DBH is discernible in cells of this group, but, in the human it is not distinguishable.

1.4. The ventral bundle and main projection fields

In all the species we have examined in the present review, TH/DBH-ir fibers form a long pair of longitudinal axon bundles running through the dorsal portion of the medulla oblongata. They run in a rostral direction through the dorsal pontine reticular formation, giving numerous labeled terminal fibers to the locus coeruleus and ventrolateral periaqueductal gray and enter to the lateral hypothalamic area. This bundle runs caudally to the spinal cord.

The PNMT-ir axon bundle is clearly distinguishable as are the TH-/DBH-ir ones in the rat. This bundle is seen as a subset of the TH-/DBH-ir one in the cat and human. In ungulates, we distinguished only a small number of PNMT-ir axons in this pathway and terminal fields. No PNMT-ir fibers were discernible in the sheep brain.

2. Pons

In this structure, most of the TH-ir neurons are also DBH-ir and are considered to be noradrenergic.

2.1. A4 cell group

This noradrenergic cell group of the cat, monkey and

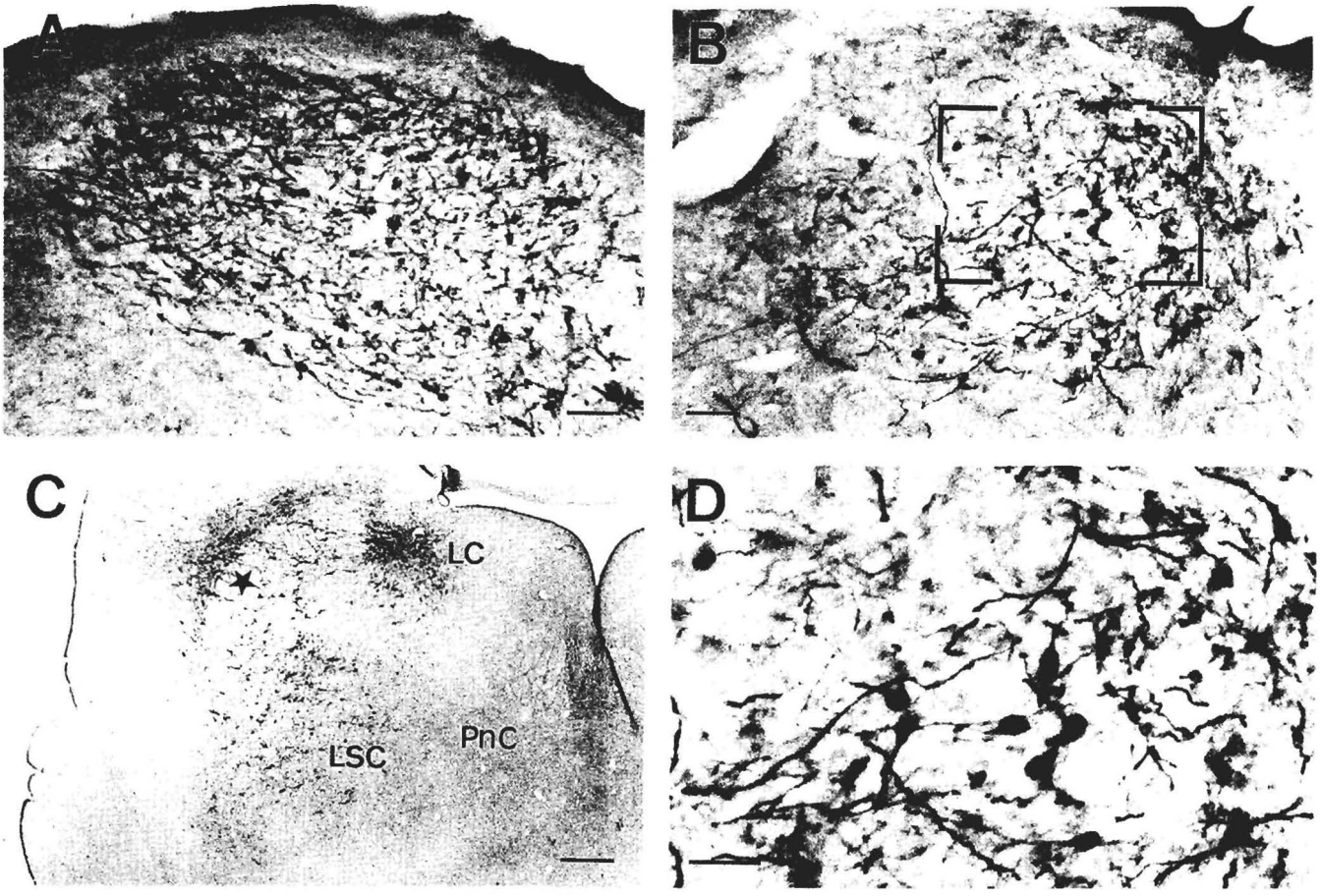

Fig. 6. A and B. Frontal sections through the dorsomedial area of the medulla oblongata, at the level of the area postrema of the sheep immunostained with a serum anti DBH (A) and a serum anti PNMT (B). Note the lower concentration of the PNMT immunoreactive neurons. **C.** DBH immunoreactive neurons in the dorsal pontine tegmentum of the sheep, at the level of the groups A6 and A7. **D.** Represents a higher magnification of B. LC: locus coeruleus; LSC: locus subcoeruleus; PnC: pontine reticular nucleus, caudal part. Star indicates the superior cerebellar peduncles. Scale bars: A, B, 100 μm; C, 50 μm; D, 750 μm.

rat is seen at the edge of the lateral recess of the fourth ventricle and is continuous with the caudal extension of the A6 locus coeruleus (LC) group. Equivalent cells are seen in the pigmented nucleus of the cerebellar tegmentum of the human (Pearson et al., 1983). It should be noted that A4 is not distinctly observable in the homologous region of the sheep, pig and cow.

2.2. A5 cell group

In the rat, A5 noradrenergic cells are seen in the ventrolateral pons, sending their axons to the dorsal vagal complex, parabrachial area, perifornical area of the hypothalamus and amygdala, and they appear to play an important but still poorly defined role in autonomic regulation (Byrum and Guyenet, 1987). In the pig, this group is composed of a small number of DBH-ir cells in an area dorsal to the superior olive. In the sheep, the A5 cell group is isolated from other groups and no DBH-ir cells are found at the level of the mid-portion of the motor trigeminal nucleus (Tillet and Thibault, 1989). In the human, DBH-ir cells are dispersed in the posterior ventral pontine reticular formation (Robert et al., 1984), but it is difficult to define this group, since it is continuous with the caudal extension of the subcoeruleus (LSC) group.

2.3. A6 and A7 cell groups

Noradrenergic cell bodies of the locus coeruleus have widespread projections to all levels of the brain (see Aston-Jones et al., 1995).

In the rat (Fig. 2A), A6 noradrenergic cells are packed to form a small cluster in the locus coeruleus (LC) in the dorsolateral pontine tegmentum, and are classified into 2 groups: dorsal (LCd) and ventral (LCv) (Swanson, 1976).

In the human brain (Fig. 2F), the LCd contains many closely packed DBH-ir neurons. A dense population of medium- to small-sized bipolar DBH-ir neurons comprises the compact core of the locus coeruleus that lies ventral and ventromedial to the mesencephalic tract of the trigeminal nerve. Scattered, large DBH-ir cell bodies lie peripheral to the main body of the locus coeruleus (Pearson et al., 1983; Kemper et al., 1987; Chan-Palay and Asan, 1989a,b, 1991; Kitahama et al., 1996). In the monkey (Fig. 2C), the distribution pattern is similar to, but more compact than that of humans.

In carnivores and ruminants, LC cells are dispersed in the pons. The feline LC complex (Fig. 2B) is of dispersed type, having a more prominent parabrachial group than rodents and primates. The A7 cell group is a rostrolateral extension of the A6 group and is localized close to the ventral tip of the brachium conjonctivum in the anterior pons. In the pig (Fig. 2E), DBH-ir neurons are also widely distributed in the pontine tegmentum. Its LCd contains only a few stained neurons, while a small cluster is seen in a region ventrolateral to the LCd. Similar results are obtained in the bovine brain (Fig. 2G) (Bérod et al., 1982), but the ventrolateral cluster is not evident.

In the sheep dorsal pontine tegmentum (Figs. 2D, 6C), DBH-ir cell bodies are close to the ventral portion of the tract of the mesencephalic nucleus of the trigeminal nerve near the medial side of the central tegmental tract and rostrally around the tract. Stained neurons are not clustered like in rats, but widely disposed in this area. In the upper pons, numerous TH-ir neurons are found near the medial border of the lemniscus lateralis and some are detected around the superior cerebellar peduncles and in the parabrachial nucleus (Tillet and Thibault, 1989).

3. Midbrain

In human and ruminants, catecholaminergic neurons are extensively dispersed in large areas of the ventral mesencephalon, unlike rats. Therefore, there are not clear-cut boundaries between the groups A8, A9 and A10.

3.1. A8 cell group

In the rat, neurons of this group are homogeneously distributed in the caudal part of the mesencephalon, in the retrorubral area, caudo-dorsal to the substantia nigra. In the retrorubral field the density of TH-ir neurons is lower in sheep (Tillet and Thibault, 1989) and pigs (Ostergaard et al., 1992) than in primates (Garver and Sladeck, 1975; Felten and Sladeck, 1983; Pearson et al., 1983). In the human, neurons of A8 are more widely dispersed than in rats (Pearson et al., 1983; Kitahama et al., 1994). TH-ir neurons of this group are observed around the red nucleus which seems "encapsulated" in pig, primate and man, but not in sheep. In this latter species, labeled neurons are not found dorsally to the red nucleus (Tillet and Thibault, 1989). Furthermore, based on the localization, we should add a complementary DA cell group in the rostral pontine reticular formation (as A8p). This group is recognized in cattle (Bérod et al., 1982) and human (Kitahama et al., 1996).

3.2. A9 cell group

The A9 cell group extends in the substantia nigra which is subdivided into three parts: the pars compacta, the pars reticularis and the pars lateralis. In all species, most of the cells are observed in the pars compacta. This group contains the greatest number of dopaminergic neurons, about 11,360-15,600 neurons in pigs (Ostergaard et al., 1992) which is greater than the 4,500-13,000 neurons observed in rats (Hedreen and Chalmers, 1972; Guyenet and Crane, 1981). The boundaries between the pars compacta and the pars reticulata are clear in sheep but less evident in pigs and human. As in primates (Arsenault et al., 1988; Haber and Groenenwegen, 1989), prominent bundles of TH-ir dendrites run through the pars reticulata in pigs

(Ostergaard et al., 1992) whereas few are observed in sheep (Tillet and Thibault, 1989). In the pars compacta, TH-ir neurons form a horizontally elongated band in all species. However, species differences exist in the pars reticulata which contains only a few isolated neurons in sheep whereas a substantial number is found in human. The dispersion of dopamine neurons in the pars compacta is slightly more important in the cow than in primates (monkey and human) (Kitahama et al., 1994). In the lateral part of the group A9, in the pars lateralis of the substantia nigra, dispersed labeled cell bodies are present, being more numerous in pig, cow and human than in sheep (Tillet and Thibault, 1989).

3.4. A10 cell group

This catecholaminergic cell group, as defined in the rat by Hökfelt et al. (1984b) is composed of different anatomically distinct areas: the ventral tegmental area (Tsaï), the central gray, Edinger-Westphal, interfascicularis and linearis, dorsal raphe and supramammillary nuclei. The greatest number of TH-ir neurons is found in the ventral tegmental area, as it contains 10,190-14,000 neurons in pigs (Ostergaard et al., 1992). Caudally, the dorso-caudal part of the group A10 (A10dc) extends in the dorsal raphe nucleus and in the ventral central gray, lying under the aqueductus cerebri. These neurons, being distinct from midbrain serotoninergic neurons, have a different morphology; serotoninergic neurons are larger than the dopaminergic ones as described in sheep (Tillet, 1987; Tillet and Thibault, 1989). This pattern of distribution is observed in all studied species but the number of labeled neurons varies according to the rostro-caudal axis. It is higher in the rostral part of the raphe nucleus in pigs and monkeys whereas in sheep and cattle, the neurons are homogeneously distributed throughout the dorsal raphe nucleus. In the ventro-rostral subdivision of the group A10 (A10vr) extending in the caudal supramammillary nucleus, only a moderate number of neurons are clearly identified in sheep and monkeys and it is difficult to distinguish in the corresponding human region. The A10 dorso-rostral cell group (A10dr), composed of a few small neurons, is observed near the habenular complex in sheep as in the rat, but this group is not described in pigs or human.

In rodents, parts of this cell group (A10dc, A10vr, A10dr) were not observed using formaldehyde-induced fluorescence (Dahlström and Fuxe, 1964), but have been described by immunohistochemistry with anti-TH (Hökfelt et al., 1984b). This observation makes questionable the true dopaminergic nature of these neurons in different species, and the presence of dopamine should be verified, since TH alone is not sufficient to synthesize dopamine.

4. Hypothalamus

In the hypothalamus, the TH-ir neurons are disposed on each side of the third ventricle, dorsally and ventrally to the ventricle. They form the groups A11 to A15.

4.1. A11 cell group

Dopaminergic neurons of this group are situated in the caudal hypothalamus around the third ventricle. This group is less extensive in pigs (Leshin et al., 1996), cattle (Leshin et al., 1995a) and sheep (Tillet and Thibault, 1989) than in rats (Hökfelt et al., 1984b). This cell group was recognized in the human fetus (Su et al., 1987) but not in the adult (Spencer et al., 1985). However, recent works have demonstrated that this cell group is present in the dorsal portion of the posterior hypothalamus (Pearson et al., 1990b). In these species, the neuronal density is lower than in rats. In the human, it extends in the caudal thalamus, unlike in rats.

4.2. A12 cell group

In the rat, the neurons of this group are distributed in the arcuate nucleus and peri-arcuate area surrounding the infundibular recess. In cattle and pigs (Leshin et al., 1995a, 1996) most of TH-ir cells lie ventrolaterally in the arcuate nucleus, whereas in sheep (Tillet and Thibault, 1989) and human (Spencer et al., 1985; Pearson et al., 1990b), they are mainly observed dorsal to the median eminence surrounding the bottom of the third ventricle. In pig, sheep, cat and cattle, an equivalent subdivision of the nucleus is not evident as reported in rodents (Hökfelt et al., 1984b) or human. In human, A12 is subdivided into two subgroups: the caudal one is seen in the tuberal region while the rostral one is found in the periventricular zone of the floor and ventral part of the wall of the third ventricle (Pearson et al., 1990b). In addition, in human, the population of TH-ir neurons is heterogeneous since the TH-ir cells situated in the ventrolateral part fail to exhibit AADC-ir (Komori et al., 1991). In fact DA-ir neurons are not observed in this area of the rat (Meister et al., 1988; Okamura et al., 1988a,b). In pig, cattle and sheep such observations have not been described. Although sheep arcuate nucleus also contains numerous AADC-ir neurons (Tillet et al., 1992), the distribution of TH-ir neurons is similar to the distribution of DA-ir neurons (unpublished data).

4.3. A13 cell group

In the rat, TH-ir neurons of this group are observed in the dorsomedial hypothalamic nucleus dorsal to the fornix, and ventrolateral to the caudal paraventricular nucleus, and the zona incerta. In pig, cattle (Leshin et al., 1995a, 1996), sheep (Tillet and Thibault, 1989) and primates (Spencer et al., 1985; Pearson et al., 1990b), this group does not extend laterally in the zona incerta as observed in rodents (Hökfelt et al., 1984b), and only a few neurons are found in the zona incerta of the cattle (Leshin et al., 1995a). In all these species, the caudal boundaries between this group and the group A11 are not easily distinguishable. In sheep, this group is

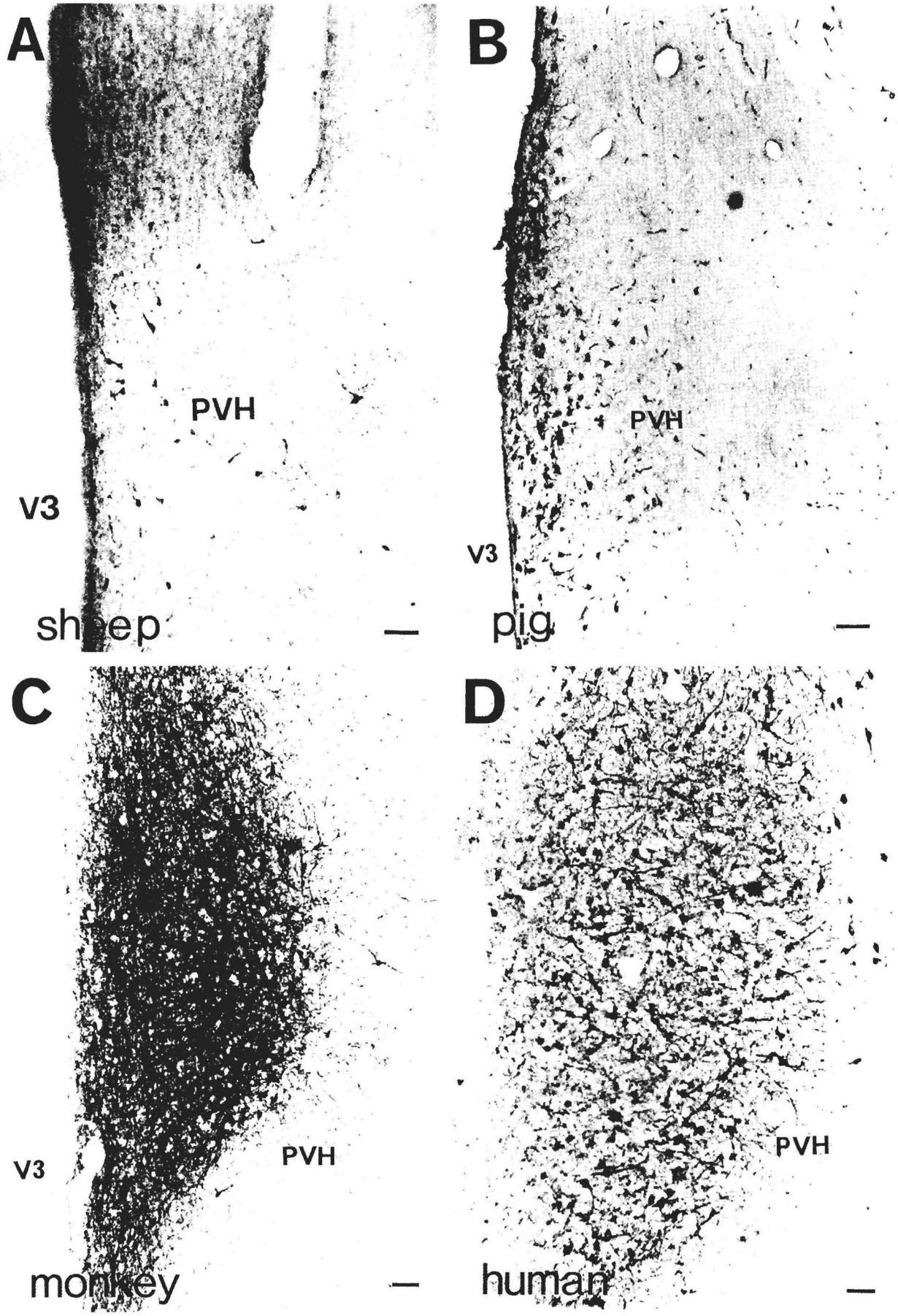

Fig. 7. TH immunoreactive neurons in the paraventricular nucleus of the hypothalamus (PVH) in sheep **(A)**, pig **(B)**, monkey **(C)** and human **(D)**. V3: third ventricle. Scale bars: 100 μm.

composed of two neuronal populations: large- and small-sized neurons are intermingled throughout the nucleus (Tillet and Thibault, 1989).

4.5. A14 cell group

These TH-ir neurons, which present a characteristic spindle-shaped form, are distributed in the anterior hypothalamus, around the third ventricle. In pig and cattle, these neurons extend from the rostral border of the median eminence to the level of the organum vasculosum laminae terminalis (OVLT) (Leshin et al., 1995a, 1996), whereas in sheep this group is not more rostral than the anterior commissure (Tillet and Thibault, 1989). In sheep, pig and cow, the A14 cell group does not present the antero-dorsal extension as described in the rodents (Hökfelt et al., 1984b); only the ventral component described in the rat is present. In these species, A14 catecholaminergic neurons are restricted to the periventricular area whereas in human they are also found in the lateral anterior hypothalamic area (Su et al., 1987; Pearson et al., 1990a). Caudally, some TH-ir neurons are dispersed in the ventrolateral hypothalamus of the rat (A14l) (Hökfelt et al., 1984b), but they are multipolar and present a shape different from those present close to the ventricle. In the pig, sheep, cattle and cat this group has not been described.

4.6. A15 cell group

This gathering of TH-ir neurons, the most recently described in rats, consists of a ventral and dorsal subgroup (Hökfelt et al., 1984b). In the rat, the ventral group is situated in the anterior hypothalamic area, including the supraoptic nucleus at the chiasmatic level, and the dorsal one in the area subjacent to the anterior commissure. In the different studied species, it is the most rostral catecholaminergic group of the diencephalon, but its shape presents several specific characteristics.

In sheep (Tillet and Thibault, 1989), pigs and cattle (Leshin et al., 1995a,b, 1996), the dorsal part is not observable and TH-ir neurons are restricted to the ventral part, in the retrochiasmatic area, where labeled neurons are intermingled with those of the accessory supraoptic nucleus (Tillet et al., 1988; Leshin et al., 1995b). The principal division of the supraoptic nucleus does not contain TH-ir neurons in cattle (Leshin et al., 1995) and they are only few in sheep and pig (Tillet, 1994; Leshin et al., 1996) (Fig. 3D, E, G). Conversely, the paraventricular nucleus of the hypothalamus contains a dense population of TH-ir neurons in pigs and cattle (Fig. 3E, G) and only few in sheep (Figs. 3D, 7).

It should be noted that in human, not only the supraoptic but also paraventricular nuclei contain numerous labeled neurons (Figs. 3F, 7D), approximately 40% of the neurons of these nuclei are TH-ir (Li et al., 1988; Panayotacopoulou et al., 1991). In other studied primates, numerous TH-ir neurons are also observed both in the supraoptic and paraventricular nuclei (Thind and Goldsmith, 1989). In the Japanese monkey (Fig. 3C), numerous TH-ir cells are observed in the paraventricular (Fig. 7C) but not in the supraotic nucleus. Because in the first description of catecholaminergic neurons using formaldehyde-induced fluorescence these neurons have not been described, the presence of dopamine in these groups remains questionable. In all these species, the A15 cell group is described by immunohistochemistry with anti-TH antibodies. In sheep, these neurons are dopaminergic, as demonstrated with antibodies raised against AADC and dopamine (Tillet al., 1990), conversely to rodents, in which some of them contain only L-DOPA (Mons et al., 1990). In cats some L-DOPA and dopamine-ir neurons are present in the dorsal and ventral parts of group A15, but only after colchicine treatment (Kitahama et al., 1990). In other species, the neurochemical content of these neurons is not determined. Neurons of the A15 cell group are magnocellular and multipolar, and, conversely to other neuronal groups, they are densely packed and their boundaries are easily distinguishable from each other. In human fetus, catecholamines are not detected in neurons of supraoptic and paraventricular nuclei using formaldehyde-induced fluorescence (Su et al., 1987; Nobin and Bjorklund, 1973). It should be necessary to study the presence of AADC in these neurons to know if they are able to synthesize dopamine.

5. Forebrain

Finally, we should note the presence of TH-ir cell bodies in the basal forebrain of primates (Köhler et al., 1983; Dubach, 1994). In fact, many of them have been demonstrated to be dopamine-immunoreactive in the monkey (Ikemoto et al., 1996). This group is not present in the rodents, and has not been described in ruminants.

Conclusion

The anatomical distribution of catecholamine neurons within identified anatomical group in ungulates and primates presents many differences when compared with rat. The nomenclature determined for the rat by Hökfelt et al. (1984b) seems not always appropriate to describe catecholaminergic neuronal systems in all the species. Many differences are found in the distribution of adrenergic/noradrenergic neurons and in the organization of hypothalamic dopaminergic neurons, between ungulates, primates and rats. In addition, catecholaminergic neurons are more loosely clustered in ungulates and primates than in rodents. Therefore identification of the boundaries between cell groups is sometimes difficult.

Ungulates present a lower density of adrenergic and noradrenergic neurons in the medulla oblongata when compared to other species. Neuronal groups are distinct from each other whereas they are found in continuity in primates (i.e. A1/A2 and A5/A6/A7). Ungulates present

a very low density of PNMT-containing neurons and in sheep only the group C2 is observable. The extension of noradrenergic neurons in the locus coeruleus of ungulates is larger than in rodents.

In the hypothalamus, ungulates and primates present a lower dopaminergic neuronal density than in rodents. The most striking difference between the ungulates and the others is observed in the rostral hypothalamus where group A14 fails to present a dorsal extension. Ungulates present only a ventral part of the group A15, whereas in primates this group is mainly localized in the supraoptic, paraventricular and accessory nuclei which exhibit a large population of TH-containing neurons, not found in other groups of mammals.

The nomenclature used to describe these catecholaminergic neuronal groups is based on TH-immunoreactivity, but several studies have demonstrated that TH-containing neurons lacking AADC synthesize only L-DOPA as observed in the A15 group of rats and parts of A12 nucleus in humans. Such TH-ir but AADC immunonegative neurons are not catecholaminergic. In this way, TH should not be used as the sole marker of catecholaminergic neurons but should be used in conjunction with other markers such as dopamine or AADC.

The present review underlines the differences observed in the catecholaminergic neuronal organization between mammalian species as suspected after the comparison found between human and rat. These differences could be considered for the environmental adaptation of the different groups of mammals. Such a comparison of the distribution of TH-containing structures or "true" catecholaminergic neurons between various species should increase our knowledge of their role in various regulations in which they are involved.

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