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ORIGINAL ARTICLE

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Nitric oxide synthase-containing neurons in the amygdaloid nuclear complex of the rat

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Abstract The nitric oxide-producing neurons in the rat amygdala (Am) were studied, using reduced nicotinamide adenine dinucleotide phosphate diaphorase (NADPHd) histochemistry. Almost all nuclei of the Am contained NADPHd-positive neurons and fibers, but the somatodendritic morphology and the intensity of staining of different subpopulations varied. The strongly stained neurons displayed labeling of the perikaryon and the dendritic tree with Golgi impregnation-like quality, whilst the dendrites of the lightly stained neurons were less successfully followed. Many strongly positive neurons were located in the external capsule and within the intraamygdaloid fiber bundles. A large number of small, strongly stained cells was present in the amygdalostriatal transition area. In the Am proper, a condensation of deeply stained cells occurred in the lateral amygdaloid nucleus. In the basolateral nucleus, the strongly NADPHd-positive neurons were few, and were located mainly along the lateral border of the nucleus. These cells clearly differed from the large, pyramidal, and efferent cells. The basomedial nucleus contained numerous positive cells but most of them were only lightly labeled. A moderate number of strongly stained neurons appeared in the medial division of the central nucleus, and a larger accumulation of strongly positive cells was present in the lateral and the capsular divisions. The medial amygdaloid nucleus contained numerous moderately stained neurons and displayed the strongest diffuse neuropil staining in Am. In the nucleus of the lateral olfactory tract, the first layer contained only NADPHd-stained axons, in the second layer, there were numerous moderately stained cells, and in the third layer, a few but deeply stained neurons. From the cortical nuclei, the most appreciable number of stained neurons was seen in the anterior cortical nucleus. The anterior amygdaloid area contained numerous NADPHd-positive neurons; in its dorsal part the majority of cells were only moderately stained, whereas in the ventral part the neurons were very strongly stained. The intercalated amygdaloid nucleus lacked NADPHd-positive neurons but an appreciable plexus of fine, tortuous axons was present. In the intra-amygdaloid part of the bed nucleus of the stria terminalis (st) some lightly stained cells were seen but along the entire course of st strongly stained neurons were observed. Some Am nuclei, and especially the central lateral nucleus and the intercalated nucleus, display considerable species differences when compared with the primate Am. The age-related changes of the nitrergic Am neurons, as well as their involvement in neurodegenerative diseases is discussed.

Keywords Amygdala · Enzyme histochemistry · Limbic system · NADPH-diaphorase · Nitrergic

Abbreviations AA: Anterior amygdaloid area · AAD: Anterior amygdaloid area, dorsal part · AAV: Anterior amygdaloid area, ventral part · ACo: Anterior cortical amygdaloid nucleus · Am: Amygdala, amygdaloid nuclear complex · AStr: Amygdalostriatal transition area · BL: Basolateral amygdaloid nucleus · BM: Basomedial amygdaloid nucleus · BST: Bed nucleus of the stria terminalis · BSTIA: Bed nucleus of the stria terminalis, intraamygdaloid division · Ce: Central amygdaloid nucleus · CeC: Central amygdaloid nucleus, capsular division · CeL: Central amygdaloid

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nucleus, lateral division · CeM: Central amygdaloid nucleus, medial division · Co: Cortical amygdaloid nuclei · DEn: Dorsal endopiriform nucleus · IM: Intercalated amygdaloid nucleus · iNOS: Inducible nitric oxide synthase · La: Lateral amygdaloid nucleus · LOT: Nucleus of the lateral olfactory tract · LOT 1: Nucleus of the lateral olfactory tract, first layer · LOT 2: Nucleus of the lateral olfactory tract, second layer · LOT 3: Nucleus of the lateral olfactory tract, third layer · Me: Medial amygdaloid nucleus · MeAV: Medial amygdaloid nucleus, anteroventral part · NADPHd: Nicotinamide adenine dinucleotide phosphate diaphorase · nNOS: Neuronal nitric oxide synthase · NO: Nitric oxide · NOS: Nitric oxide synthase · OT: Optic tract · PB: Phosphate buffer · PBS: Phosphate buffered saline · Pir: Piriform cortex · PLCo: Posterolateral cortical amygdaloid nucleus · PRh: Perirhinal cortex · st: Stria terminalis · VEn: Ventral endopiriform nucleus

Introduction

Nitric oxide (NO) is a gaseous neuromediator, apparently released as soon as synthesized (Bredt and Snyder 1992; Snyder 1992; Vincent and Hope 1992; Dawson and Snyder 1994; Vincent 1994; Garthwaite and Boulton 1995). It diffuses rapidly and influences NO-responsive target cells probably within surprisingly extended spatial limits of ~0.3–0.4 mm (Lancaster 1997). Thus, though NO-producing cells are scarcely spread in many regions, the NO released may influence neurons in a widely extended area (Prast and Philippu 2001). As a freely diffusible molecule, NO does not require a synaptic contact to exert its effects, although recent evidence suggests that it may act preferentially at the synapse (Valtschanoff and Weinberg 2001; Burette et al. 2002). The formation of NO is carried out by nitric oxide synthase (NOS), the enzyme responsible for the calcium/calmodulin-dependent formation of citrulline and nitric oxide from arginine. Reduced nicotinamide adenosine dinucleotide phosphate diaphorase (NADPHd) was introduced as histological marker that stains certain neurons with a Golgi-impregnation-like quality (Thomas and Pierce 1964; Vincent 1986; and references therein). Following the discovery that neuronal NOS (NOS-I) is an NADPHd (Dawson et al. 1991; Hope et al. 1991; Schmidt et al. 1992), both reinterpretations of the already published neuroanatomical and neuropathological data, and numerous new findings appeared rapidly (see Fig. 1 in Weinberg et al. 1996a). Mappings of the CNS distribution of NADPHd/NOS (Vincent et al. 1983a, b; Mizukawa et al. 1989; Valtschanoff et al. 1992, 1993a, b; Vincent and Kimura 1992; Geula et al. 1993; Johnson and Ma 1993; Onstott et al. 1993; Egberongbe et al. 1994; Rodrigo et al. 1994, 2006; Vizzard et al. 1994; Blottner et al. 1995; Leonard et al. 1995; Satoh et al. 1995; Sobreviela and Mufson 1995; Vincent 1995; Bertini and Bentivoglio 1997; Bidmon et al. 1997; Kharazia et al. 1997; Iwase et al. 1998; Oerman et al. 1998; Downen et al. 1999; Paxinos et al. 1999; Usunoff et al. 1999, 2003; Lazarov 2002; Garbossa et al. 2005; Gotti et al. 2005) consistently show that this enzyme appears in groups of neurons that cannot be defined by other anatomical criteria (perikaryal size, somatodendritic morphology, neuronal connectivity, etc.). NOS-positive neurons are to be found throughout the neuraxis, from the cerebral cortex to the spinal cord, as well as in the sensory and autonomic ganglia. They might be robust projection cells, and small local circuit neurons. The basic transmitter of NOS-positive neurons is most often GABA but it might be also acetylcholine, as well as several neuropeptides.

The amygdaloid nuclear complex (Am) is a relatively voluminous gray substance, located in the depth of the ventromedial temporal lobe, ventral to the caudolateral striatum and to the pallidum. It is a highly heterogeneous structure and consists of several nuclei, divided on the basis of cytoarchitectonic, hodological, histochemical, and immunohistochemical studies (reviewed in Price et al. 1987; de Olmos 1990, 2004; Amaral et al. 1992; McDonald 1992, 2003; Pitkänen 2000; Swanson 2003; de Olmos et al. 2004). The Am has diverse afferent and efferent connections throughout the CNS, and is involved in the modulation of neuroendocrine functions, visceral effector mechanisms, and in complex patterns of behavior: learning and memory, aggression and defense, pain modulation, reproduction, food intake, etc. (for comprehensive reviewes see Eleftheriou 1973; Ben-Ari 1981; Aggleton 1992, 2000). In addition, Am is significantly involved in severe neurologic and psychiatric diseases.

Some of the above mentioned mappings noticed NOS-containing neurons in Am, and several investigations were focused on the Am (Sims and Williams 1990; Pitkänen and Amaral 1991; Brady et al. 1992; Unger and Lange 1992; McDonald et al. 1993; Leontovich et al. 2004; Ashwell et al. 2005; Olmos et al. 2005; Menendez et al. 2006). Here, we present a precise mapping of NOS-containing cells and fibers in the Am of the rat that extend the data available.

Material and methods

Ten young-adult male Wistar rats, weighing 260–300 g, were used. The experiments were carried out following the Bulgarian and German regulations on animal welfare in conformance to National Institutes of Health guidelines. Under deep ether anesthesia, the animals were perfused transcardially with 150 ml 0.05 M phosphate buffered saline (PBS), followed by 500 ml fixative solution containing 4% paraformaldehyde and 0.1% picric acid in 0.1 M phosphate buffer (PB), pH 7.3. Two hours after the end of the perfusion, the brains were removed and postfixed overnight in 4% paraformaldehyde in the same buffer at 4°C. The brains were blocked

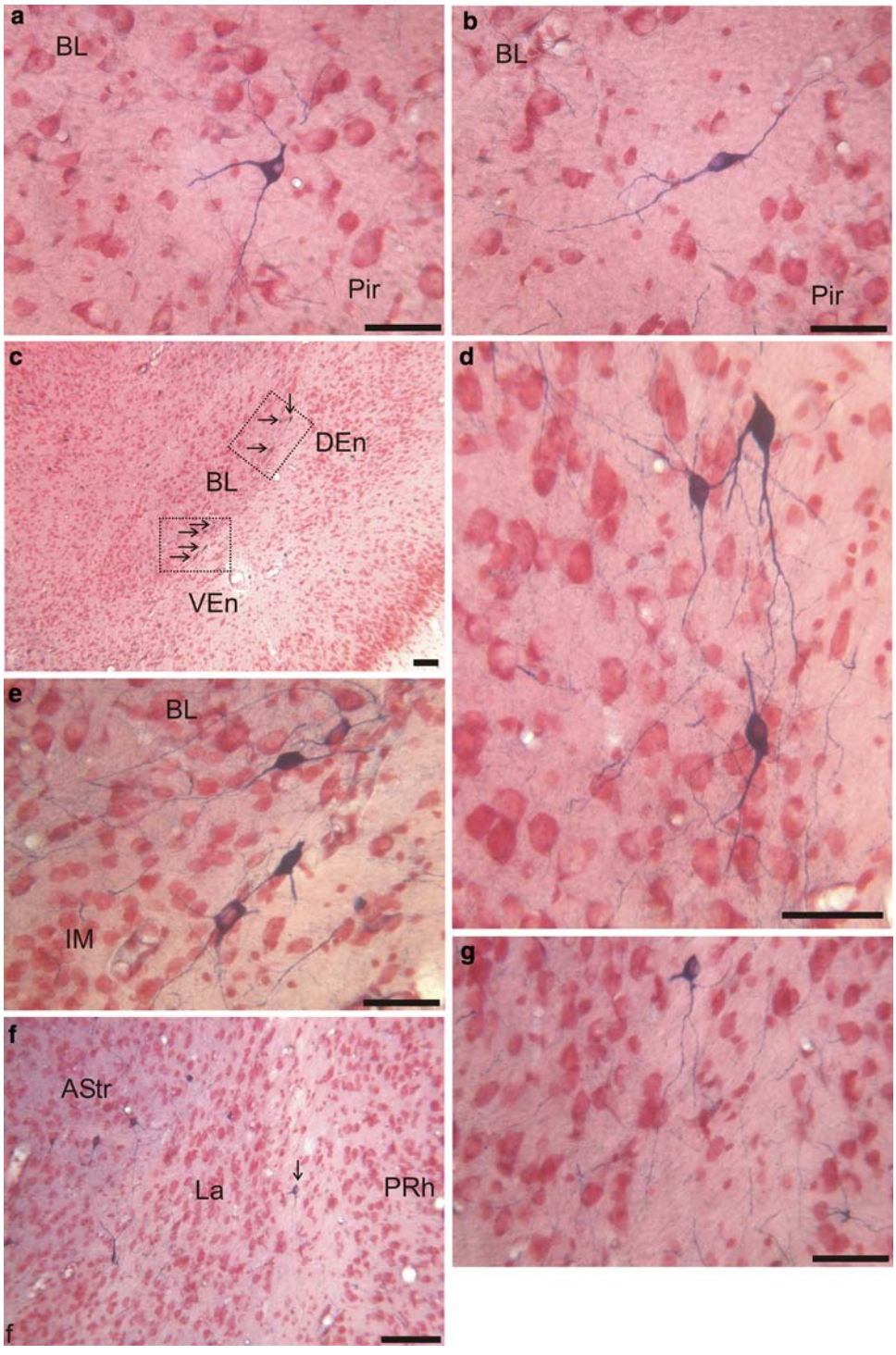

Fig. 1 Border cells located in the external capsule, separating the basolateral amygdaloid nucleus (*BL*) and the piriform cortex (*Pir*). **a** Multipolar neuron with radiating dendrites. The dorsally oriented dendrites reach the BL territory. **b** Elongated neuron with two long, sparsely branching dendrites. **c–e** Border cells in the external capsule, separating BL and the endopiriform nuclei. **c** Low power overview. *DEn* dorsal endopiriform nucleus, *VEn* ventral endopiriform nucleus. **d–e** Details from **c** to **d** Medium-sized labeled cells at the lateral border of BL. **e** Elongated border cells with dorsoventrally oriented dendrites. The cell-poor zone to the right is the external capsule, separating BL from DEn. **f–g** Border cells in the external capsule, separating the lateral amygdaloid nucleus (*La*) and the perirhinal cortex (*PRh*). **f** Low power overview. *AStr* amygdalostriatal transition area. The *arrow* points to a border cell enlarged in **g**. **g** Oval neuron with slender, long, ventrally oriented dendrites. *Scale bars*: 100 μm

in the coronal ($n = 8$), sagittal ($n = 1$), and horizontal ($n = 1$) planes and were immersed in 0.1 M PB containing 20% sucrose for 48 h. Serial 30 μm thick sections were cut on a "Reichert Jung" freezing microtome and were collected in PB. Every eighth section was stained for NADPHd, employing a modification of the procedure of Scherer-Singler et al. (1983). Free floating sections were incubated for 30 min in 0.1 M Tris–HCl buffer, pH 7.4 with 0.8% Triton X-100, and then incubated for 90 min in 20 ml 0.1 M Tris–HCl buffer (pH 7.4) containing 8 mg reduced nicotinamide adenine dinucleotide phosphate (Sigma, St. Louis, MO, USA) and 20 mg nitroblue tetrazolium (Sigma). The sections were washed in PBS, mounted on chrome-gelatin-coated slides, air dried and counterstained with 1% neutral red to enhance cytoarchitectonic orientation, and to compare the NADPHd-positive and -negative neuronal populations. In addition, adjacent sections were stained

with cresyl violet. The atlases of Swanson (1992), Paxinos and Watson (1998), and Paxinos et al. (1999) were consulted to aid in assignment of nuclear borders. For investigation of the specificity of the histochemical staining by the first two cases, control sections were treated identically except for the omission of the substrate, and the result was negative. The sections were observed with a Leitz Aristoplan microscope. Photomicrographs of selected fields were taken with a digital camera (7.3 three Shot Colour, Visitron Systems, Munich, Germany; Diagnostic Instruments).

Results

The present results on the distribution and cytological characteristics of NADPHd-positive neurons in the Am (as well as in the thalamus and striatum) are very similar to those observed in our previous study on the thalamus and brain stem (Usunoff et al. 1999), obtained by the histochemical method of Weinberg et al. (1996a), and by immunocytochemistry for NOS, using the primary antiserum anti-NOS I, characterized in Schmidt et al. (1992). Neuronal perikarya, dendrites and axons were stained, and the cell nuclei remained unstained. The glial and endothelial cells were unstained. We found no interindividual variability in the presently reported ten experiments.

Nicotinamide adenine dinucleotide phosphate diaphorase-positive cells and fibers were present in almost all divisions of Am but their number, cytological characteristics and intensity of labeling varied significantly.

The ''border cells'', located in the external capsule, separating the basolateral amygdaloid nucleus (BL) and the piriform cortex (Pir) (Fig. 1a–b), the BL and the endopiriform nuclei (Fig. 1c–e), and the lateral amygdaloid nucleus (La) and the perirhinal cortex (Fig. 1f–g) were most conspicuous. ''Border cells'' were also observed within the thin white matter laminae that separated individual nuclei of Am (Fig. 2a). Such neurons were always strongly positive. The perikarya were elongated or more rarely multipolar. The dendrites were long, straight and branched infrequently.

The large condensation of NADPHd-positive neurons was observed in the amygdalostriatal transition area (AStr), wedged between the La and BL laterally, and central lateral (CeL) medially (Fig. 2a, b). The cells were small, round or oval and always deeply stained and often, the slender, sparsely branched dendrites could be followed for a considerable distance. Apparently, the dendrites of these neurons radiate in all directions, since such ''unipolar'' neurons (Fig. 2b) were very common also in sagittal and horizontal sections. Therefore, many stained dendritic fragments were present in the neuropil. The latter contained an extremely dense network of NADPHd-stained fine terminal varicose fibers with very thin intervaricose portions (Fig. 2b). Among them thicker parent NADPHd-positive axons were also seen.

In the Am ''proper'' [Am excluding the transitional areas and the intraamygdaloid portion of the bed nucleus of the stria terminalis (BST)] a large density of strongly stained neurons was encountered in La (Fig. 2a, c–e). Weakly NADPHd-stained cells were absent in this nucleus. The cells were small to medium-sized, and deeply stained. The perikarya were oval and elongated and gave rise to wavy dendrites that could only rarely be followed for a long distance. Fragments of stained dendrites were very common (Fig. 2c). A characteristic feature of the neuropil was the presence of a substantial number of stained axons that sometimes formed loose bundles, especially close to the borders of the nucleus (Fig. 2c, e).

The BL contained a small number of NADPHd-positive neurons that were, however, always strongly stained. The great majority of them were located in the peripheral portion of BL, close to the external capsule (Figs. 1d, 2f, g). Only occasional NADPHd-stained neurons were present in the central portion of the nucleus (not shown). The cells were oval or elongated, and generally smaller than the majority of BL neurons that are the largest cells of the Am. The slender, wavy dendrites rapidly disappeared from the section. Probably they are considerably long because, contrary to the paucity of stained perikarya, numerous NADPHd-positive dendritic fragments appeared in the neuropil. The latter contained an abundant plexus of thin NADPHd-stained axons (Fig. 2g).

In the basomedial amygdaloid nucleus (BM) numerous NADPHd-positive neurons were present, regularly dispersed throughout the nucleus but only few of them were strongly stained (Fig. 3a). Such neurons had an oval or elliptical perikaryon with several dendrites, sometimes with a robust initial dendritic trunk. The majority of NADPHd-labeled perikarya displayed a pale staining of the thin cytoplasmic rim, surrounding the unstained nucleus. The dendrites of these cells could usually be followed for a short distance, and then on, with difficulty. The neuropil contained a very dense network of thin NADPHd-positive axons but the image was obscured by a diffuse neuropil staining, although it was not so strong as in other nuclei. The diffuse blue neuropil coloration (Pitkänen and Amaral 1991) is not clearly associated with any neural structure.

All three divisions of the central amygdaloid nucleus (Ce)—medial (CeM), lateral (CeL), and capsular (CeC)—contained a moderate number of NADPHd-positive neurons. In CeM the labeled cells were medium-sized, multipolar, with several thin, long dendrites (Fig. 3b, c). Only few labeled thin axons were observed in the neuropil. A somewhat larger number of NADPHd-labeled neurons were found in CeL. The cells were irregularly distributed. In some sections (especially in the caudal part of CeL) only occasional neurons were labeled, whilst in other cases the NADPHd-stained neurons appeared in groups (Fig. 3d, e). The round or oval perikarya were small to medium-sized, and deeply stained. The dendrites were thin, straight and long, and

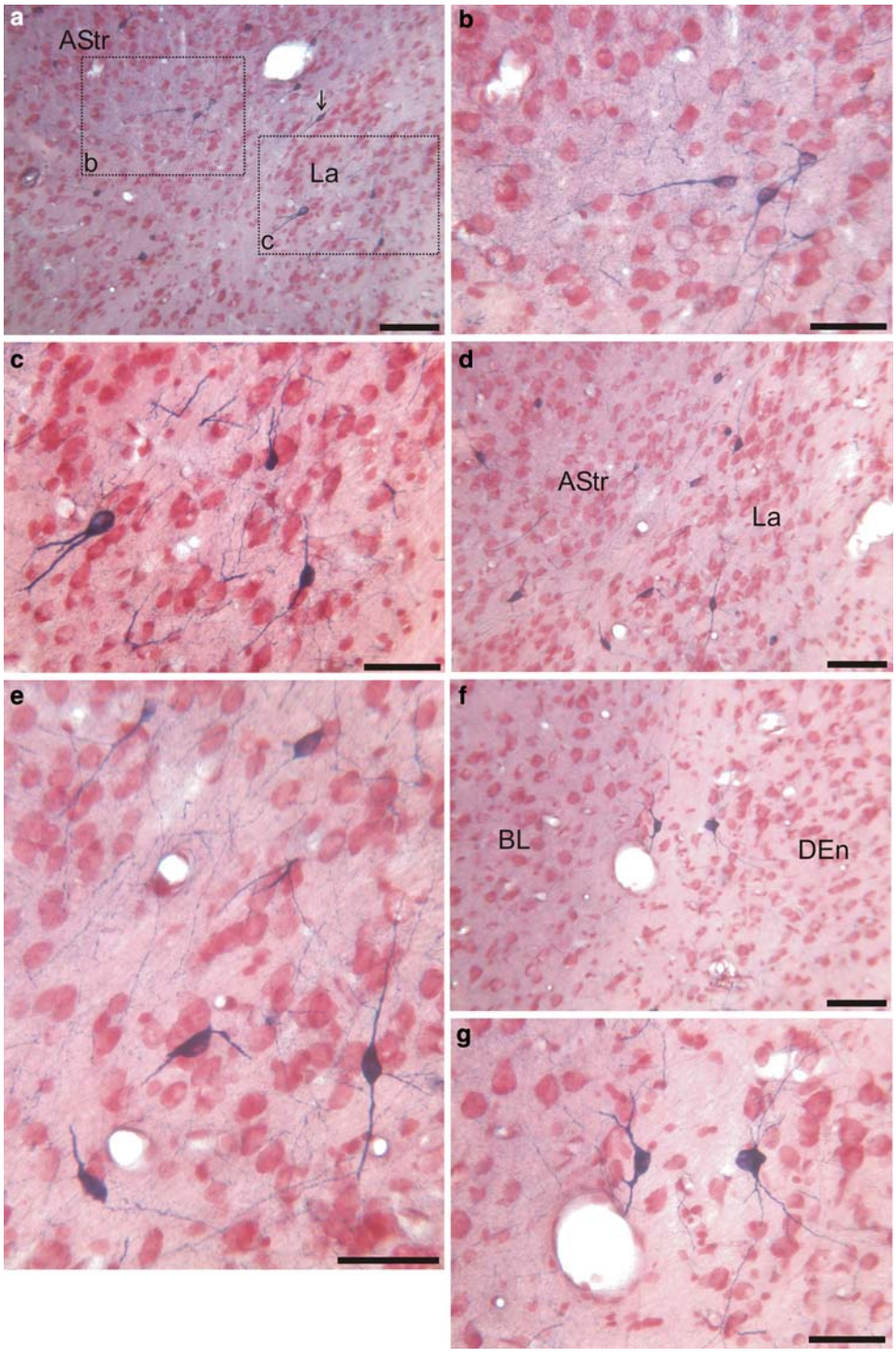

Fig. 2 **a** Low power overview of portions of AStr, La, and central lateral nucleus (*CeL*). The *arrow* points to a border cell between AStr and La. **b–c** Details from **a**. **b** Group of NADPHd-positive neurons in AStr. The dendritic arborization is hard to be followed. Dense plexus of fine NADPHd-stained fibers in the neuropil. **c** NADPHd-positive perikarya and initial portions of their dendrites in La. Numerous dendritic fragments and fine axons in the neuropil. **d–e** Densely arranged NADPHd-stained neurons in La. **d** Low-power overview. **e** Detail from **d**. Group of elongated neurons in La. The neuropil contains numerous stained axons and dendritic fragments. **f–g** Border zone between BL and DEn with two deeply stained neurons. Note an obvious difference between the density of the stained fine fibers in the neuropil of the two nuclei. **g** Detail from **f**. Scale bars: 100 μm

usually disappeared rapidly from the section. The neuropil contained a substantial number of fine varicose NADPHd-stained axons. Compared to the low density of the neuronal population in CeC, the number of NADPHd-positive cells appeared not to be small (Fig. 3f). The small to medium-sized neurons were deeply stained. The perikarya emitted two to several dendrites (Fig. 3g, h). Often the initial dendritic trunk was relatively thick. The secondary dendrites were thin, long, and branched infrequently. The tertiary dendrites were extremely thin. The neuropil contained a dense plexus of fine tortuous axons.

A large number of NADPHd-positive cells was observed in the medial amygdaloid nucleus (Me), especially in its medial amygdaloid nucleus anteroventral part (MeAV) (Fig. 4a, b). The cells were small, with round perikarya. Some neurons were strongly stained but the majority of cells displayed a moderate staining of the

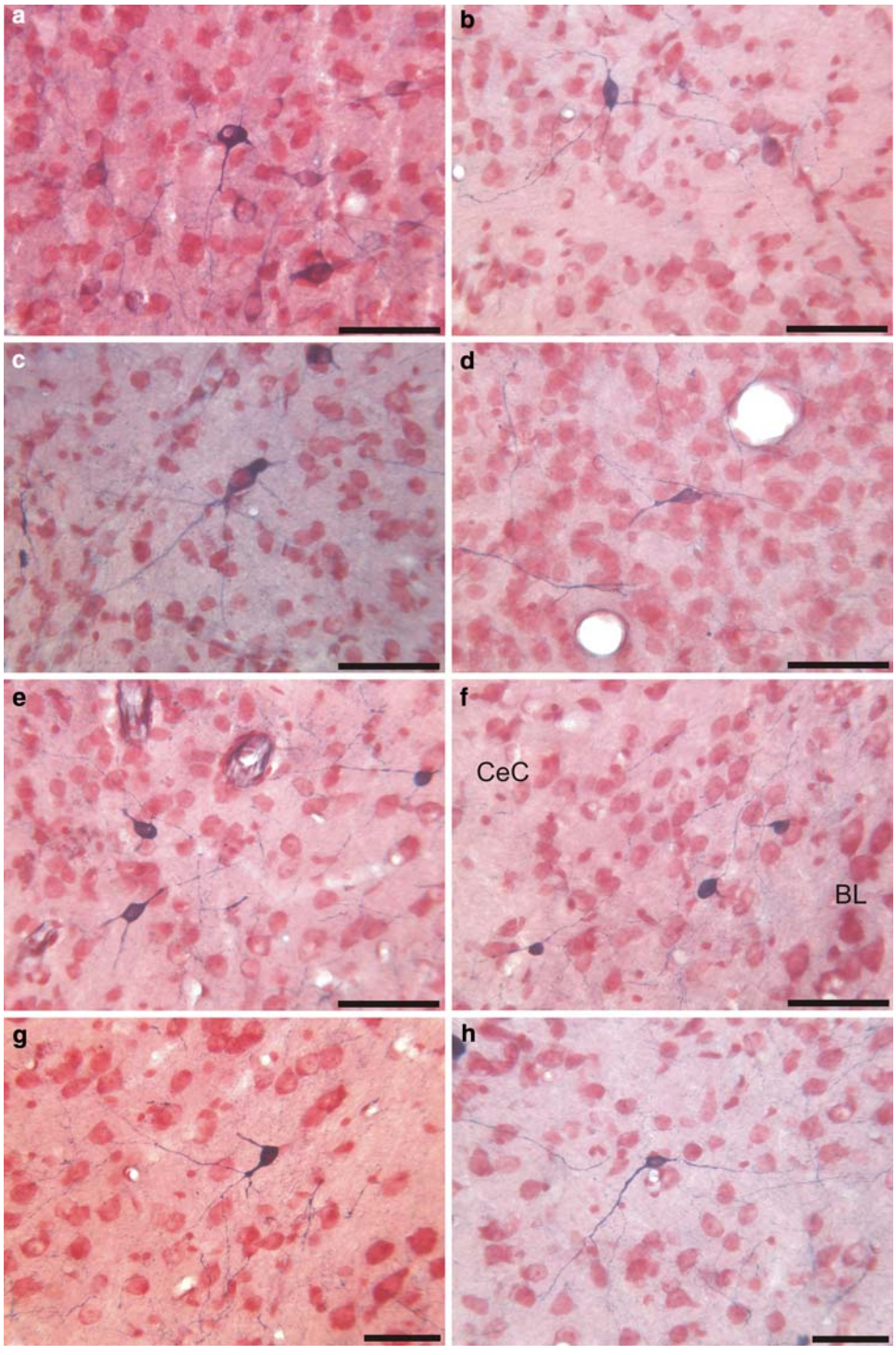

Fig. 3 **a** NADPHd-stained neurons in the BM. Few medium-sized neurons are deeply stained, while the majority of small and medium-sized neurons are only lightly stained. **b–c** Medium-sized, slightly elongated, strongly stained neurons in CeM. The long dendrites can be followed for a considerable distance (**b**). The neuropil contains only a loose plexus of stained fine axons. **d–e** NADPHd-stained neurons in CeL. **d** A solitary stained elongated neuron in the caudal portion of the CeL. The neuropil contains fragments of stained dendrites and numerous fine terminal axons. **e** Three deeply stained cells in the anterior portion of CeL. A dendrite of one of the cells is followed for a considerable distance but most of the dendrites disappear rapidly from the plane of sectioning. Note a very dense plexus of stained fine axons. **f–h** NADPHd-positive neurons in CeC. **f** Three deeply stained small, oval cells located close to the border with BL (large neurons at the lower right corner). **g**, **h** Solitary, deeply stained cells in CeC. Also the distal dendritic ramifications are seen. Numerous fine, tortuous labeled axons are seen within the neuropil. Scale bars: 100 μm

scant cytoplasm. Only the proximal portions of the primary dendrites were visualized. In Me, the most strong diffuse staining of the neuropil was present.

The nucleus of the lateral olfactory tract (LOT) displayed significant differences of NADPHd staining in its three layers (Fig. 4c). The nucleus of the lateral olfactory tract, first layer (LOT 1) contained no NADPHd-positive perikarya, and in the neuropil very few labeled fine, tortuous axons were seen. The nucleus of the lateral olfactory tract, second layer (LOT 2) contained a considerable number of moderately stained round cells. In the neuropil, there was a strong diffuse labeling, comparable to that in Me. In the nucleus of the lateral olfactory tract, third layer (LOT 3), a moderate number of strongly stained neurons was seen (Fig. 4d). The cells were medium-sized, multipolar, with distinct dendritic

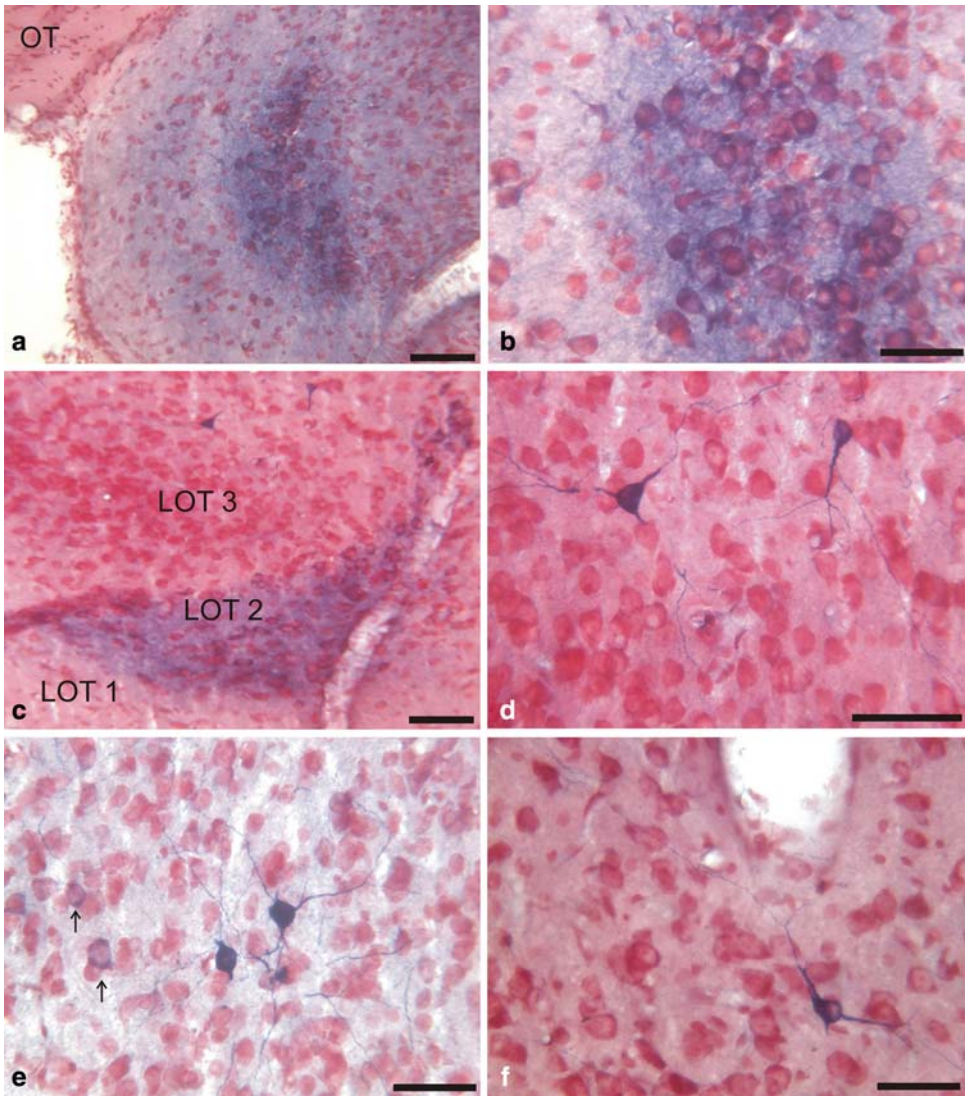

Fig. 4 **a–b** NADPHd-stained neurons and neuropil in MeAV. **a** Low-power overview of MeAV. The strong neuropil staining is visible also by small magnification. *OT* optic tract. **b** Detail from **a**. Within the band of strong neuropil staining the great majority of small, round neurons display a moderate to strong NADPHd-labeling. **c–d** NADPHd-stained neurons in LOT. **c** Low-power overview demonstrating the significant differences of perikaryal and axonal staining in the three layers. **d** Detail from **c**. Two strongly stained neurons with long, slender dendrites in LOT 3. **e–f** NADPHd-positive neurons in Co. **e** Two strongly stained round neurons with long dendrites in ACo. Several lightly stained cells are also seen (*arrows*). There are numerous stained dendritic fragments in the neuropil but the axonal labeling is moderate. **f** A deeply stained neuron in PLCo. The secondary dendrites are thin and long. Scale bars: 100 μm

poles. The dendrites were long and with a wavy course. The neuropil contained a moderate number of NADPHd-positive fine fibers.

The cortical amygdaloid nuclei (Co), and especially the anterior nucleus (ACo), followed by the posterolateral nucleus (PLCo) contained deeply stained medium-sized multipolar neurons (Fig. 4e, f) that gave rise to long, wavy, sparsely branched dendrites. ACo contained also lightly stained perikarya with unlabeled dendrites (Fig. 4e). The neuropil contained few labeled fine fibers.

In the anterior amygdaloid area (AA) an appreciable number of NADPHd-stained neurons were encountered. In the anterior amygdaloid area, dorsal part (AAD) the NADPHd-positive neuronal population was heterogeneous: medium-sized to small moderately stained multipolar and oval perikarya (Fig. 5a). The larger neurons had distinct primary dendritic trunks and thin, long, sparsely branched secondary dendrites. The neuropil contained a moderate number of stained fine axons. The NADPHd-labeled neurons in the anterior amygdaloid area, ventral part (AAV) were medium-sized and deeply stained (Fig. 5b, c). The oval or elongated perikarya gave rise to tortuous dendrites that rapidly disappeared from the plane of the section (Fig. 5b). Some neurons emitted long, markedly varicose dendrites with thin intervaricose portions (Fig. 5c). In the neuropil numerous stained dendritic fragments and relatively few NADPHd-positive axons were encountered.

The intercalated amygdaloid nucleus (intercalated cell masses, ''massa intercalata'', IM) contained the smallest neurons of the Am (Fig. 5d). IM contained no NADPHd-stained neurons but in the neuropil a substantial plexus of thin, varicose-labeled axons was seen (Fig. 5e, f). In addition, dendrites of adjacent ''border cells'' in CeC were observed to invade the IM (Fig. 5g).

The intraamygdaloid division of the bed nucleus of the stria terminalis (BSTIA) contained a few NADPHd-positive neurons (Fig. 6a). The cells were small, round, moderately stained, and the dendrites could be followed for only a short distance. The stria terminalis (st)

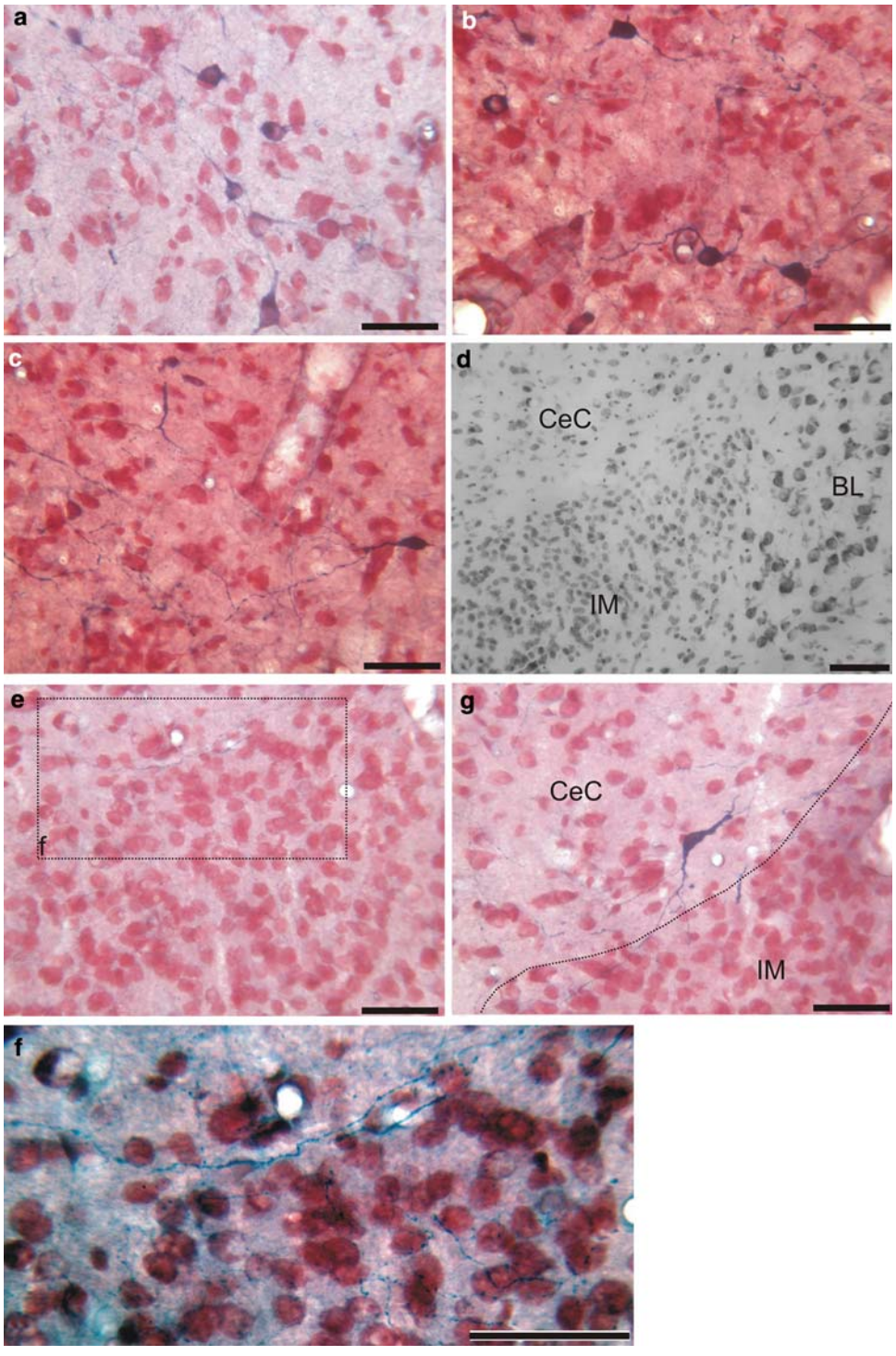

Fig. 5 **a–c** NADPH-d staining in AA. **a** Several small to medium-sized, moderately stained neurons in AAD. **b**, **c** Deeply stained neurons in AAV. The cells in **b** display thin, tortuous dendrites, and the neuron in **c** emits markedly varicose dendrites. **d–g** Nissl and NADPHd staining of IM. **d** Cresyl violet-stained section, adjacent to the section, presented in **e**. The small neurons of IM are located close to the large-sized neuronal population of BL. **e** The neurons in IM lack NADPHd labeling but the neuropil contains a substantial number of NADPHd-stained fine, varicose axons. **f** derived from **e**. The *blue* channel of this image has been selectively enhanced with regard to contrast to visualize the weakly NADPHd-stained axons. **g** Border zone between CeC and IM. A strongly stained CeC neuron sends its dendrites within the IM territory. Scale bars: 100 μm

contained solitary NADPHd-positive neurons along its entire course (Fig. 6b–d). Such cells were small to medium-sized, and were always strongly stained. The perikaryon emitted thin dendrites that were difficult to follow. The NADPHd-stained axons in st at its exit from the Am occupied its medial part (Fig. 6b), and in the supracapsular part of st shifted ventromedially (Fig. 6c). The proper BST contained few NADPHd-positive neurons, similar to those observed in BSTIA.

Discussion

Cytoarchitecture and topical distribution of the nitrergic neurons in Am

We here present a comprehensive description of nitric oxide producing neurons in the nuclei of the Am that extend previously reported data.

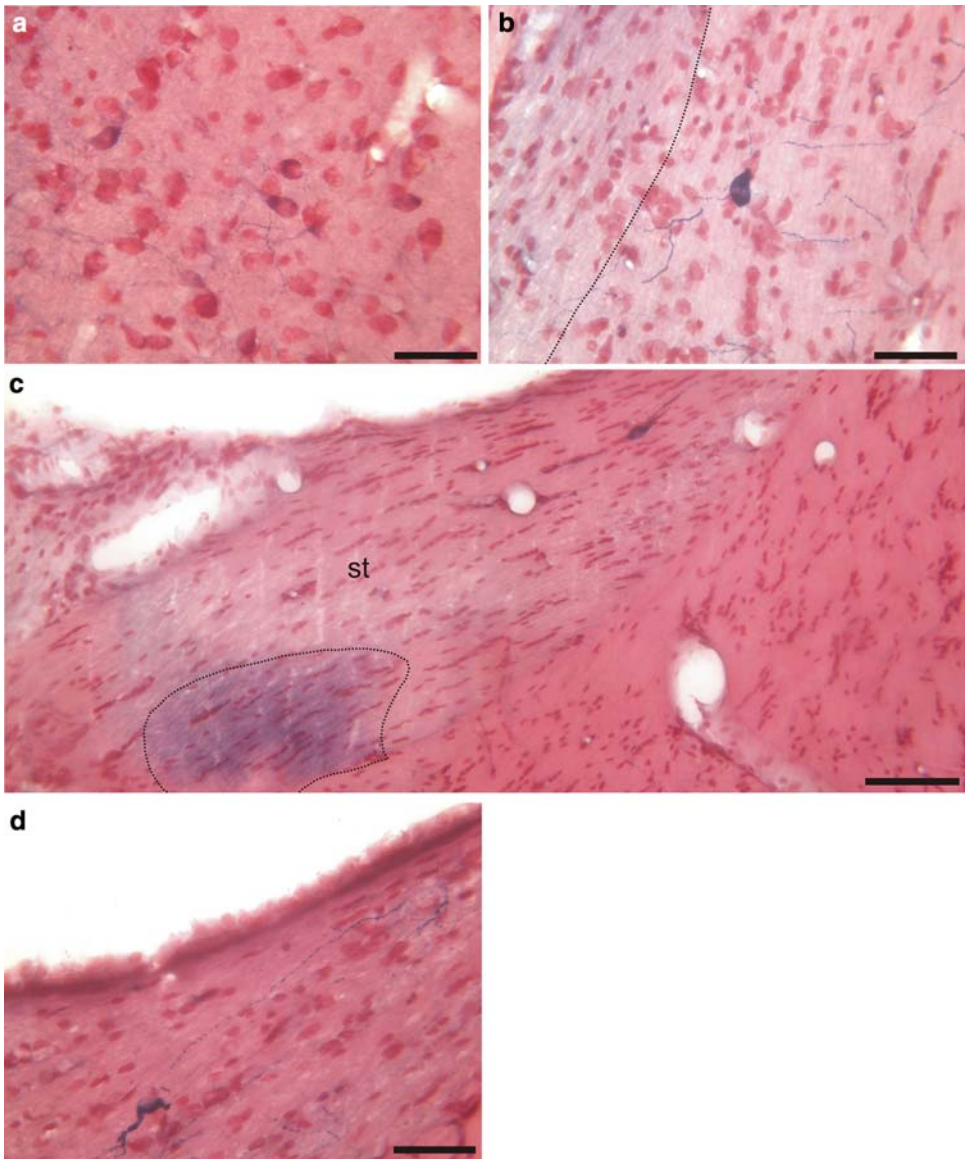

Fig. 6 NADPHd-stained neuronal elements in BSTIA and st. **a** Small, moderately stained neurons in BSTIA. **b** Medium-sized, deeply stained neuron in st at its exit from Am. Numerous stained dendritic fragments. The *dashed line* demarcates the NADPHd-stained axons in the medial part of the st. **c** Supracapsular part of st. A strongly stained medium-sized neuron in its lateral part. The *dashed line* demarcates the NADPHd-stained axons in the ventromedial part of st. **d** A medium-sized, deeply stained neuron in st that starts its prethalamic descent. A long, straight, varicose dendrite is also seen. The NADPHd-stained axons are intermingled with unstained fibers. Scale bars: 100 μm

Most characteristic are the border cells located in the fibrous layers separating the Am from surrounding structures, as well as in the bundles, separating the individual nuclei of the Am. Such cells were invariably strongly stained, indicating a significant production of nitric oxide. The border cells are medium-sized and most of them have elongated perikarya that give rise to several very long, sparsely branched, and spine-free dendrites. These neurons were first thoroughly described by McDonald et al. (1993) and they noticed that the dendrites of the border cells invade both adjacent regions. The plottings of Pitkänen and Amaral (1991) and of Satoh et al. (1995) suggest that border cells are common also in the monkey Am, moreover Pitkänen and Amaral classify them as type 1 cells, e.g., neurons with a deeply stained perikaryon and dendrites. The transmitter characteristics and connections of the border neurons remain to be elucidated. Their somatodendritic morphology resembles the isodendritic neurons of the brainstem reticular formation (Leontovich and Zhukova 1963; Ramon-Moliner and Nauta 1966). For decades Leontovich insists that reticular neurons are present also in the basal forebrain, and recently she described such neurons also in the Am (Leontovich et al. 2004, see Fig. 5a, A1).

A large density of perikaryal and axonal NADPHd staining was observed in the Astr. The NADPHd-positive neurons are small with divergently radiating dendrites, so that often the perikarya appear as "unipolar". When compared with the adjacent striatum, some of the NADPHd neurons there are larger and regularly emit several strongly stained dendrites. According to Alheid et al. (1995) and de Olmos et al. (2004) the cell population of Astr consists of neurons that are smaller, more loosely packed and more lightly stained than those in remaining striatum—a statement well confirmed by the

observation of cresyl violet stained sections in the present study. In the striatum, the NADPHd-positive cells are the third type of aspiny interneurons that contain also several peptides (Vincent et al. 1983a, b; Kowall et al. 1987; Kawaguchi 1993; Kawaguchi et al. 1995; Gerfen 2004). In all probability, the NADPHd-positive cells in the Astr are also local circuit neurons. Moreover, they are most typical non-pyramidal cells, as defined by McDonald et al. (1993). It should be noted that the homogeneous AStr in the rat differs from the same structure in higher species (Mai et al. 2003; reviewed in de Olmos 2004). Fudge and Haber (2002) reported that in macaques the lateral Astr is "striatal like", whilst the medial Astr is more related to Ce than to the striatum. Thus, one might expect that future studies on the primate Astr will present data on the topographic distribution of the NOS-containing neuronal elements.

Several studies agree that La contains the highest number of strongly NADPHd-stained neurons. It appears that this finding is common throughout the phylogenetic scale, since it was reported in echidna (Ashwell et al. 2005), mouse (Olmos et al. 2005), rat (McDonald et al. 1993; the present study), monkey (Pitkänen and Amaral 1991; Brady et al. 1992; Satoh et al. 1995), and human (Brady et al. 1992; Leontovich et al. 2004). The cells observed by us were generally small and oval, and the neuropil was filled with stained dendritic fragments, as well as with a considerable number of stained axons. These cells belong to the group of non-pyramidal neurons of the basolateral nuclear complex, as classified by McDonald et al. (1993). Probably these cells are GABAergic local circuit neurons that also contain calcium-binding proteins (Kemppainen and Pitkänen 2000; McDonald and Mascagni 2001; and references therein). The production of nitric oxide in La appears to be higher in primates. Similar to McDonald et al. (1993) we observed only a population of deeply stained neurons. However, in monkey and human La also a significant number of weakly positive neurons are present (Pitkänen and Amaral 1991; Brady et al. 1992).

In the BL a significant number of NADPHd-positive cells were reported in the monkey (Pitkänen and Amaral 1991; Brady et al. 1992), most of which are moderately stained. Similarly, Ashwell et al. (2005) described abundant lightly stained neurons in the BL of the echidna. In the rat both the number of NADPHd-positive neurons and the intensity of staining are different. We observed a limited number of positive neurons but all were deeply stained. Only very few NADPHd-positive cells were seen in the central part of BL, whereas most of the stained neurons were observed in the most peripheral portions of BL, close to the border cells. Such distribution was demonstrated also by McDonald et al. (1993). The NADPHd-stained neurons (and especially the small, centrally located cells) are clearly different from the main, efferent neuronal type in BL: large, pyramidal, probably glutamatergic neuron (reviewed in McDonald 1984, 1992). The BL contains ~7–10% small interneurons, regularly dispersed through the nucleus (see Fig. 12 in McDonald 1984). The larger, often elongated NADPHd-positive neurons observed by us may correspond to the type II (larger interneurons) described by McDonald (1984). According to him, ~15–18% are not class I cells (large, projection neurons). Since the number of NADPHd-stained neurons in BL is quite small, one might speculate that only a subset of the interneuronal population in the BL of the rat synthesizes nitric oxide. Recently McDonald and Mascagni (2002) demonstrated that there are at least three major subpopulations of GABAergic interneurons in BL that contain different neuropeptides and calcium-binding proteins. In all probability, the axons of the NADPHd-positive interneurons branch profusely, since we observed an extremely dense plexus of NADPHd-positive terminal axons in BL.

McDonald et al. (1993) plotted only few strongly labeled cells in BM, located mainly peripherally. We observed a moderate number of deeply stained neurons by which also secondary dendrites could be followed. However, we observed numerous lightly stained small cells too. There was also a significant diffuse neuropil staining, although not so strong as in Me and LOT 2. The strongest diffuse staining of BM, is demonstrated by Paxinos et al. (1999). On their figures, this staining delineates sharply the borders of the nuclei. However, the nature of the diffuse labeling including electron microscopic observations of Weinberg et al. (1996b) is a matter of debate, which is beyond the scope of the present study.

We observed a moderate number of densely stained medium-sized neurons in CeM. According to McDonald et al. (1993), only the initial portion of the dendritic arborization of these neurons was clearly visualized. Such is the neuron shown in Fig. 3d. However, in some fortunate cases (Fig. 3b) we were able to follow the dendrites of CeM neurons for a long distance. McDonald et al. (1993) suggest that the NADPHd-positive neurons in CeM might be cholinergic. This proposal should be accepted with some caution. There are numerous investigations on the cholinergic neuronal elements in Am (reviewed by de Olmos 2004; Usunoff et al. 2006b) but only few studies report the presence of cholinergic neurons in Am (Carlsen and Heimer 1986; Nitecka and Frotscher 1989; Lolova and Davidoff 1990; Butcher et al. 1992; Phelps et al. 1992; Heckers and Mesulam 1994; Asan 1998), and only Nitecka and Frotscher (1989) and Asan (1998) demonstrated choline acetyltransferase-immunopositive perikarya in CeM. According to Nitecka and Frotscher (1989), these cholinergic neurons are closely related to the most prominent cholinergic population—the basal magnocellular nucleus of Meynert in the substantia innominata (the Ch4 group of Mesulam et al. 1983).

We encountered an appreciable number of NADPHd-positive neurons and a dense fiber plexus in CeL and CeC, which is agreement with McDonald et al. (1993). McDonald et al. (1993) observed lightly stained cells in CeL but in our material there were also

representative, deeply stained, neurons. Interestingly, Pitkänen and Amaral (1991) reported that CeL of *Macaca fascicularis* is almost free of positive cells and fibers. Brady et al. (1992) also found only a few lightly stained cells in CeL of the squirrel monkey but demonstrated an appreciable number of strongly positive neurons in human CeL. This species difference is difficult to be explained. Since Hall (1972a, b), investigations of various species agree that CeL is closely related to the ventral putamen (reviewed by McDonald 1992), where numerous NADPHd-positive neuronal elements are present.

Similar to many previous studies, we found a large concentration of NADPHd-positive neurons in Me, and especially in MeAV. These densely packed small cells, with moderately stained scant cytoplasm, are projection neurons. Tanaka et al. (1997) found out that ~40% of the Am neurons projecting into the paraventricular hypothalamic nucleus are nitrergic cells, and 16% of NADPHd-positive neurons in Me project into the paraventricular nucleus. Thus, at least a part of NADPHd-stained axons in st originate in Me.

The nucleus of the lateral olfactory tract was only briefly mentioned by McDonald et al. (1993). We presently describe a complicate pattern of NADPHd staining in its three layers. LOT 1 contained only few positive axons. LOT 2 contained numerous moderately stained perikarya and a very strong diffuse neuropil staining, whilst in LOT 3 there were comparatively few NADPHd-positive cells that were always deeply stained. Probably, the latter correspond to the darkly stained type 1 cells observed in the monkey's LOT by Pitkänen and Amaral (1991).

The Co in the monkey contains almost exclusively lightly NADPHd-stained neurons (Pitkänen and Amaral 1991; Brady et al. 1992) that are at variance with the rat. The drawings of McDonald et al. (1993) suggest that Co contain deeply stained cells. This is in agreement with the present data. In all subdivisions of Co, and especially in ACo, followed by PLCo, we observed an appreciable number of strongly stained medium-sized perikarya, emitting several long dendrites. The principal neurons of the Co are spiny pyramidal neurons that closely resemble those of the adjacent piriform cortex and BL (Hall 1972a; McDonald 1992). The presently observed NADPHd-positive neurons are non-pyramidal cells, and in all probability are local circuit neurons.

The anterior amygdaloid area attracted little attention in previous studies. The drawings of Pitkänen and Amaral (1991) and of Brady et al. (1992) suggest that the monkey AA contains predominantly lightly labeled cells. We observed a substantial number of NADPHd-positive neurons in AA. In AAD, the small and medium-sized perikarya were moderately labeled but the dendrites of larger cells could be followed to secondary branchings. The strongly stained medium-sized neurons in AAV are among the most conspicuous NADPHd-labeled cells in the Am. It appears that there are two varieties of such cells. The first, a more common variety, comprises multipolar neurons with radiating, wavy dendrites. The second type is the elongated neurons with long, markedly varicose dendrites. The connectivity and transmitter characteristics of these two varieties remain to be elucidated.

By the IM, there is a significant species difference. Pitkänen and Amaral (1991) documented a large number of type 3 (lightly labeled) neurons in the monkey IM. We never observed an NADPHd-positive perikaryon on IM territory, but a plexus of tortuous fine axons and "invading dendrites" of cells in the neighboring nuclei were invariably present. The IM is a striatal-like structure. The small cells with dendrites densely covered with dendritic spines resemble smaller versions of the medium-sized spiny neurons of the striatum and CeL (McDonald 1992). Hence, the IM neurons should have a significant nitrergic innervation, as it is in the striatum (Mizukawa et al. 1989; Vincent and Kimura 1992; Geula et al. 1993; Wu and Parent 2000; Johannes et al. 2003). Apparently in the rat it is carried out by nitric oxide producing neurons outside of IM.

We observed NADPHd-positive neurons in BST, in BSTIA, and along the entire course of st, which is in agreement with McDonald et al. (1993). The NADPHd-stained neuronal population was not uniform. The cells in BSTIA and in BST were moderately stained, with largely unlabeled dendrites. In contrast, in the initial portion of st, in the supracapsular BST (cf. Alheid et al. 1998; Shammah-Lagnado et al. 2000), as well as in the terminal (prethalamic) portion of st, the medium-sized neurons were always very strongly stained and emitted long dendrites that, however, were hard to follow from the parent perikaryon. The position of NADPHd-stained axons within st was characteristic. By its exit from the Am, the nitrergic fibers were located in the medial part of st, by the supracapsular course they shifted ventromedially, and in the terminal part, they did not form a compact bundle.

Nitrergic neurons of the Am in physiology and pathology

The non-demented elderly persons display mild changes in the Am, only the Me and Co nuclei are more severely affected (Mann et al. 1990; Mann 1992). By normal aging, the human Am decreases linearly with age, and these changes do not differ from those observed in adjacent gray masses, and there are no sex differences (Allen et al. 2005). Similarly, the Am and hippocampus of aged mice showed small, insignificant reductions in total neuronal numbers but the number of degenerated axons increased (von Bohlen und Halbach and Unsicker 2002). The age related changes of nitric oxide producing neurons in the Am were investigated in humans (Unger and Lange 1992) and in rats (Joo et al. 2004). Unger and Lange (1992) noticed only insignificant atrophic alterations of NADPHd-stained neurons and fibers. Joo et al. (2004) report that nNOS immunoreactive neurons are decreased in almost all Am areas in aged rats, but the

nNOS immunoreactivity of the neuropil is increased in Am nuclei related with main and accessory olfactory systems. We studied the age related changes in nuclei containing a large density of NADPHd-positive neurons: in the laterodorsal tegmental, and pedunculopontine nuclei (Lolova et al. 1996, 1997), and in the dorsolateral column of the periaqueductal gray (Lolova et al. 1999, 2000). Similar to the data obtained for Am, we observed no cell loss in the laterodorsal and pedunculopontine nuclei, and a minimal cell loss in the periaqueductal gray. However, many neuronal perikarya were atrophic, some were hypertrophic, and the dendrites underwent significant degenerative changes such as local swelling, shrinkage, folding, and in 26-month-old rats the occurrence of dendritic stumps was very common. Thus, the nitrergic neurons in diverse brain areas appear to be among the survivors in advanced aging.

The Am is included in nociceptive multineuronal chains (reviewed in Gauriau and Bernard 2002; Price 2002; Neugebauer et al. 2004; Usunoff et al. 2006a, b). Presently, the laterocapsular part of Ce is defined as the ''nociceptive Am'' because of its high content of nociceptive neurons (Bourgeais et al. 2001; Gauriau and Bernard 2002; Li and Neugebauer 2004; Neugebauer et al. 2004). Immediately after the definition of nitric oxide as a gaseous neuromediator, the first data on it stated that it is involved in nociceptive processing (Meller and Gebhart 1993). Later, its profound role in nociception in the peripheral nervous system was firmly established (Steel et al. 1994; Salter et al. 1996; Aley et al. 1998; Gordh et al. 1998; Mayer et al. 1999; Zimmermann 2001; Yeo 2002; Buzzi and Moskowitz 2005; Jansen-Olesen et al. 2005; Zochodne and Levy 2005; Ding and Weinberg 2006; to cite only a few). The role of nitric oxide in the central somatosensory system is less elucidated. Shaw and Salt (1997) found that iontophoretically applied nitric oxide donors can potentiate transmission in the ventrobasal thalamus. Moreover, nitric oxide levels in the rat thalamus are dependent on its behavioral state, raising the possibility of this agent modulating the sensory alertness (Williams et al. 1997). Krukoff and Khalili (1997) examined the stress-induced activation of nitric oxide-producing neurons in the rat brain. They visualized nitric oxide histochemically, and the activation of the neurons was assessed according to the expression to the neuronal expression of the immediate early gene c-fos. The largest percentage of double-stained neurons (46%) was found in basolateral Am. Okere et al. (2000) described that a subcutaneous capsaicin injection in rats raises the production of nitric oxide in Me. Echeverry et al. (2004) and Guimaraes et al. (2005) also pointed out that stress induces activation of NOS-containing neurons in rat's Me. Interestingly, although CeL and CeC contain the bulk of nociceptive Am neurons, and these nuclei contain an appreciable number of nitrergic neurons, there are still no data on their activation during nociceptive processing.

The Am is deeply involved in several severe neurologic and psychiatric diseases, such as Alzheimer' disease and related neurodegenerative diseases (Brockhaus 1938; Herzog and Kemper 1980; Unger et al. 1988, 1991; Brady and Mufson 1990; Esiri et al. 1990, 1997; Emre et al. 1993; Kromer Vogt et al. 1990; Braak and Braak 1991; Mann 1992; Benzing et al. 1993; Vereecken et al. 1994; Braak et al. 1996; Schmidt et al. 1996; Jellinger and Bancher 1998; Chow and Cummings 2000; Shibuya-Tayoshi et al. 2005), in Huntington's chorea (Zech et al. 1986; Mann et al. 1993; Rosas et al. 2003), in temporal lobe epilepsy (Bruton 1988; Feindel and Rasmussen 1991; Gloor 1992; Hudson et al. 1993; Honavar and Meldrum 1997; Wolf et al. 1997; Pitkänen et al. 1998; Thom et al. 1999; Aliashkevich et al. 2003; Pitkänen 2004), in schizophrenia (Bogerts 1993; Bogerts et al. 1993; Roberts et al. 1997; Shenton et al. 2001), in bipolar disorder (Haldane and Frangou 2004), and in autism (Amaral et al. 2003; Bauman and Kemper 2003, 2005).

Already in the classical description of the NADPHd-stained neurons (Thomas and Pearce 1964), it was noticed that the ''solitary active cells'' are resistant to damage. This was confirmed repeatedly in the striatum by Huntington's chorea (Ferrante et al. 1985; reviewed by Mitchell et al. 1999; Deckel 2001), and in Parkinson's and Alzheimer's disease the nitrergic striatal neurons are also spared, although they appear shrunken or bulbous with foreshortened dendritic processses (Mufson and Brandabur 1994). Due to Alzheimer's disease, the number of NADPHd-positive neurons within the substantia innominata even increases (Benzing and Mufson 1995). It is well known that in Alzheimer's disease, the basic neuropathologic phenomenon is the severe degeneration of the forebrain cholinergic system (Mesulam's groups Ch1–Ch4). However, the pontomesencephalic cholinergic system (groups Ch5, Ch6) does not degenerate (Woolf et al. 1989). One of the possible explanations of this resistance is that the pontomesencephalic cholinergic neurons are the best nitric oxide producing cells within the CNS (Vincent et al. 1983b; Vincent 2000; Usunoff et al. 2003), whilst the human forebrain cholinergic neurons do not produce nitric oxide (Geula et al. 1993). There are numerous data indicating that the nitrergic neurons are involved in schizophrenia (Akbarian et al. 1993a, b; Garcia-Rill et al. 1995; Karson et al. 1996; Bernstein et al. 1998, 2001; Baba et al. 2004; Lauer et al. 2005), and the altered structures are strikingly diverse: cholinergic neurons of the pedunculopontine nucleus, cerebellum, hypothalamic paraventricular nucleus, prefrontal, and temporal cortex, and striatal interneurons.

The pathological alterations of the nitric oxide producing neurons in Am attracted less attention. Contrary to the considerable body of literature on the Am pathology in Alzheimer's disease, until recently, the only study on this problem was the observation of Unger and Lange (1992) that there were no differences when comparing NADPHd staining in regions that contained numerous neuritic plaques (accessory basal nucleus)

with areas that were relatively free of lesions (lateral nucleus). Katsuse et al. (2003) studied the expression of NOS in brains of patients with dementia with Lewy bodies, and compared it with brains of patients with Alzheimer's dementia, as well as with non-demented elderly persons. They found an overexpression of inducible NOS (iNOS) in Am but in contrast, the expression of neuronal NOS (nNOS) in Am was reduced, especially in brains showing severe Lewy pathology. The data on nitric oxide producing Am neurons by epilepsy are even more scant. Talavera et al. (1997) examined the NADPHd-stained Am, hippocampal and striatal neurons after experimental epilepsy in rats. They found a selective increase in number and density of lightly labeled Am neurons, while the deeply stained Am neurons did not change. Interestingly, despite the growing evidence for the involvement of nitrergic neurons in schizophrenia, there are still no data on eventual changes of the nitric oxide producing neurons of the Am in this disease.

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