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Immunohistochemical distribution of neuropeptides in the amygdaloid complex of the cat. A comparative study in mammals

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SUMMARY

The distribution of several neuropeptides in the amygdaloid complex of the cat is described. Five of the neuropeptides studied (luteinizing hormone-releasing hormone, β-endorphin, dynorphin A (1-17), γ-melanocyte-stimulating hormone or galanin) did not show immunoreactive profiles, whereas neuropeptide Y and somatostatin displayed the widest distribution throughout the amygdaloid nuclei. The medial amygdala (medial nucleus, medial division of the central nucleus) contained the highest number of the neuropeptides studied, whereas the lateral nucleus displayed the lowest amount of immunoreactive profiles. In addition, the morphological data suggest the possible co-existence of several neuropeptides in the same fibers and/or cell bodies, and a comparison with previous studies on the projections of the amygdaloid nuclei in the cat allows us to speculate about the possible peptidergic content of these pathways. The distribution of the neuropeptides studied in the cat is compared with the location of the same peptides in the amygdaloid complex of other mammalian species. Finally, the possible physiological functions of the neuropeptides, as well as aspects of future research into the morphology of neuropeptides in the cat amygdala are discussed.

Key Words : Neuropeptides – Cat – Amygdaloid complex

INTRODUCTION

The amygdaloid nuclear complex is a heterogeneous region that has been implicated in a variety of functions. It is critical for producing appropriate emotional and behavioral responses to biologically relevant sensory stimuli and constitutes an essential link between the sensory and limbic areas of the cerebral cortex and subcortical brain regions such as the hypothalamus, brainstem, and striatum, which are responsible

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for eliciting emotional and motivational responses (McDonald, 1998). It has been described that amygdala lesions prevent the acquisition of fear responses (Collins and Pare, 2000), suggesting the involvement of the amygdala in the expression and learning of fear. Indeed, fear is correlated to an increase of the firing rate of the lateral nucleus neurons (Collins and Pare, 1999; Pare and Collins, 2000), and it has been described that the lateral nucleus is the input station of the amygdala for conditioned fear stimuli, whereas the central amygdaloid nucleus is the output station for conditioned fear responses (Collins and Pare, 1999). In addition, the lateral amygdaloid nucleus is endowed with an inhibitory gating mechanism that regulates the flow of information through the amygdala (Lang and Pare, 1997; Lang and Pare, 1998).

On the other hand, predatory attack behavior, elicited in the cat by electrical stimulation of the lateral hypothalamus, is powerfully suppressed by the medial amygdala (Han et al., 1996 b), and it has been demonstrated that the basal amygdala facilitates defensive rage (Siegel et al., 1997). Other studies have reported that stimulation of the central nucleus of the amygdala induces significant increases in systemic arterial blood pressure (Baklavadzhyan et al., 2000). This nucleus also modulates the transmission of impulses in an ascending pulpal (nociceptive) information to the first somatosensory cortex (Kawarada et al., 1996). Finally, another amygdaloid subdivision, the basolateral amygdala, could contribute to forming the individual characteristics of higher nervous activity (Merzhanova et al., 2000), and should be regarded as a structure determining the individual typological characteristics of the animal's behavior (Merzhanova et al., 1998). The functional importance of the amygdaloid complex is also demonstrated by the fact that deficiencies in the performance of the amygdala contribute in part to the appearance of several neurological disorders, including Alzheimer's and Huntington's diseases (De Olmos, 1990).

Some of the physiological functions in which the amygdala has been implicated are also carried out by several neuropeptides. For example, substance P has been implicated in the stimulation of predatory attack behavior (Han et al., 1996 a; Han et al., 1996 b); substance P and enkephalins have different effects on defensive rage (Gregg and Siegel, 2001; Siegel et al., 1997), and calcitonin gene-related peptide and neuropeptide Y have cardiovascular actions (Chronwall et al., 1985; Gray and Morley, 1986; Skofitsch and Jacobowitz, 1985). In addition, the elicitation of analgesia has been reported for gastrin-releasing peptide/bombesin (Panula et al., 1982); and enkephalins are involved in nociception (Matsumoto et al., 1992). These and other biologically active peptides have been detected by means of immunohistochemical or radioimmunoassay techniques in the amygdaloid complex of several species, including the rat (Benoit et al., 1982; De Quidt and Emson, 1986; Haring et al., 1991; Matsumoto et al., 1992; Palkovits, 1988; Panula et al., 1982; Skofitsch and Jacobowitz, 1985), the monkey (Amaral et al., 1989; McDonald et al., 1995), and humans (Benzing et al., 1992; Bouras et al., 1987; Walter et al., 1990; Zaphiropoulos et al., 1991). However, only scarce data are available on the distribution of neuropeptides in the amygdala of the cat (Rao et al., 1986; Shaikh et al., 1993; Siegel and Schubert, 1995; Siegel et al., 1997). Substance P has been detected in neurons of the medial amygdaloid nucleus (Shaikh et al., 1993), and adrenocorticotropin-like immunoreactivity has been observed in fibers of the anterior amygdaloid area, the medial division of the central nucleus, and the medial nucleus of the cat amygdaloid complex (Rao et al., 1986). No detailed studies on the distribution of neuroactive substances were carried out in the cat amygdaloid complex until 1998 (see Marcos et al., 1998; Marcos et al., 1999).

Recently, the anatomical distribution of fibers and cell bodies containing several neuropeptides has been described in the cat amygdala using immunohistochemical methods (Marcos et al., 1998; Marcos et al., 1999). These substances include neurokinin A (NKA), β-endorphin (END), α-and γ-melanocyte-stimulating hormone (α-and γ-MSH), leucine-enkephalin (LEU-ENK), methionine-enkephalin-Arg^6-Gly^7-Leu^8 (MET-ENK), dynorphin A (1-17) (DYN), gastrin-releasing peptide/bombesin (GRP), calcitonin gene-related peptide (CGRP), luteinizing hormone-releasing hormone (LHRH), somatostatin (SOM), neuropeptide Y (NPY), galanin (GAL), and neurotensin (NT). Since morphological and physiological studies addressing the neuropeptides in the amygdala of the cat have increased the last two decades, we found it interesting to 1) review the morphological data that, at the present, we have about the distribution of neuropeptides in the amygdaloid complex of the cat; 2) compare the distribution of neuropeptides in the cat amygdala with those observed in the amygdaloid complex of other mammalian species; and 3) analyse possible neuropeptide-containing pathways in the cat amygdala.

Neuropeptide distribution in the cat amygdala

Mapping of the different neuropeptides was performed according to the stereotaxic atlas of Jasper and Ajmone-Marsan (Jasper and Ajmone-Marsan, 1966). Figure 1 shows the morphology

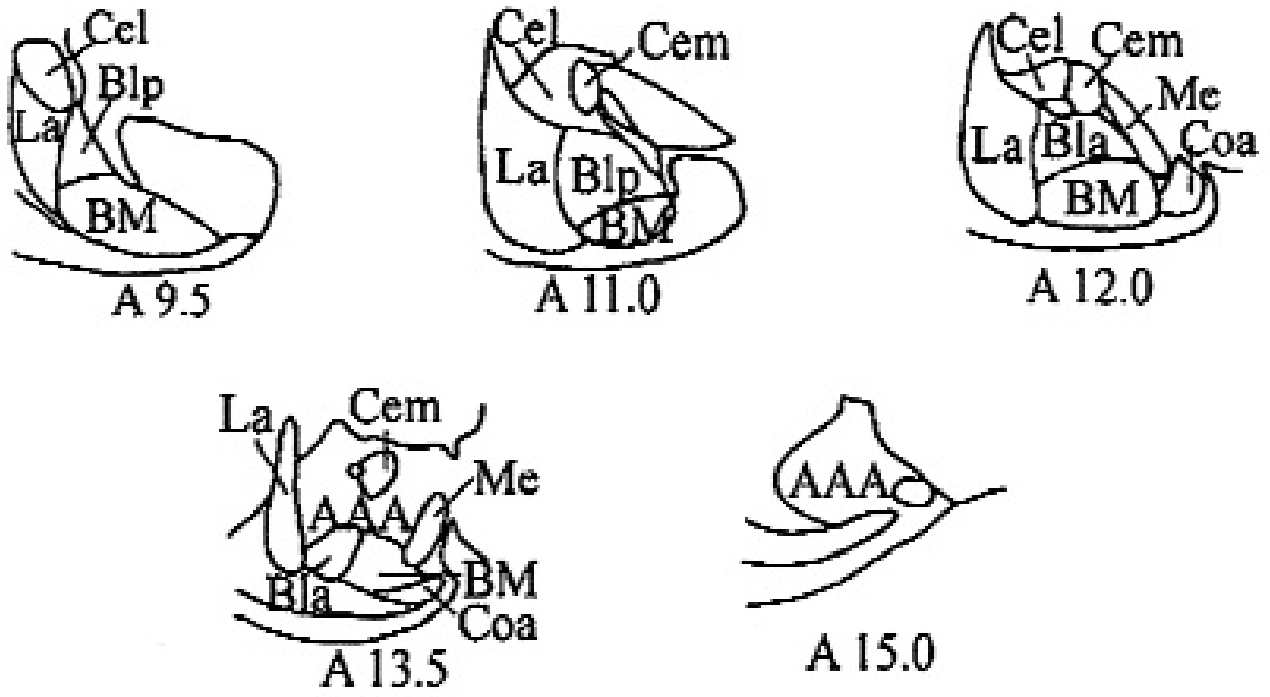

Fig. 1.- Different caudo-rostral levels of the amygdaloid complex of the cat, corresponding to the Jasper and Ajmone-Marsan (Jasper and Ajmone-Marsan, 1966) stereotaxic atlas. Anteriority (A) with respect to the zero stereotaxic point is indicated in mm.

of the amygdaloid complex. The nomenclature of the anatomical structures was derived from Krettek and Price (Krettek and Price, 1978). The cat amygdala was devoid of LH-RH, END, DYN, γ-MSH or GAL (Marcos et al., 1998; Marcos et al., 1999). Concerning the remaining studied neuropeptides, their distribution throughout the amygdaloid complex of the cat is summarised in table 1, and described in detail in the following sections.

Anterior amygdaloid area (AAA)

In this amygdaloid region, fibers displaying NEO-END, NKA, NT and MET-ENK were found at a low density, whereas SOM and NPY were present in fibers at a moderate density. Immunoreactive perikarya contained SOM (moderate density; 10-20 cell bodies per section), or NPY (low density, < 10 cell bodies per section) (Marcos et al., 1998; Marcos et al., 1999). In addition, adrenocorticotropin-like (ACTH-like) immunoreactive fibers were also detected in this region (Rao et al., 1986).

Anterior division of the basolateral nucleus (Bla)

A low density of fibers immunoreactive for NKA, MET-ENK, or CGRP was detected in this region, as well as a moderate density of fibers containing SOM or NPY. These two neuropeptides were also present in perikarya, at a low density for SOM and at a moderate density for NPY (Marcos et al., 1998; Marcos et al., 1999). In this nucleus, cell bodies and fibers containing parvalbumin (PV) have also been described (Smith et al., 1998).

Posterior division of the basolateral nucleus (Blp)

A similar distribution of immunoreactive cell bodies and fibers was observed in this nucleus and in the Bla (Marcos et al., 1998; Marcos et al., 1999; Smith et al., 1998).

Anterior cortical nucleus (Coa)

In this nucleus, a moderate density of fibers containing SOM, NKA, NPY or GRP was found, as well as scarce fibers immunoreactive for MET-ENK. Cell bodies were stained for NPY or CGRP at a low density, and a moderate density of SOM-positive perikarya was also detected (Marcos et al., 1998; Marcos et al., 1999).

Posterior cortical nucleus (Cop)

A similar neuropeptide distribution was detected in the Cop and in the Coa (Marcos et al., 1998; Marcos et al., 1999).

Basomedial nucleus (BM)

A low density of immunoreactive fibers for α-MSH, NKA and CGRP was observed in this nucleus, as well as a moderate density of SOM-positive and NPY-containing fibers. Immunoreactive cell bodies in this nucleus contained SOM (low density) or NPY (>20 cell bodies per section, high density) (Marcos et al., 1998; Marcos et al., 1999).

Medial division of the central nucleus (Cem)

Seven of the eleven neuropeptides studied were observed in fibers of this amygdaloid region. NKA, MET-ENK, and CGRP were found at a low density, and NT and LEU-ENK were present at a moderate density. SOM and NPY displayed high densities in immunoreactive fibers. Only NPY was found at a moderate density of immunoreactive perikarya (Marcos et al., 1998; Marcos et al., 1999). Enkephalinergic cell bodies (Siegel et al., 1997) were present in Cem, as well as fibers positive for adrenocorticotropin (Rao et al., 1986).

Lateral division of the central nucleus (Cel)

The density of immunoreactive fibers observed in this nucleus was low for the following neuropeptides: NT, LEU-ENK, MET-ENK, NPY, and CGRP. A moderate density was detected in the case of SOM. Concerning cell bodies, a low density of SOM- or LEU-ENK-immunoreactive perikarya was found in this nucleus, and a moderate density of NPY-positive cell bodies (Marcos et al., 1998; Marcos et al., 1999). Enkephalinergic perikarya have been observed in this nucleus (Siegel et al., 1997).

Medial nucleus (Me)

Six neuropeptides were present at low density in immunoreactive fibers: SOM, NKA, LEU-ENK, MET-ENK, GRP and CGRP. A moderate density was found only in the case of NPY. This neuropeptide was also observed at a moderate density in cell bodies, as well as GRP. In this nucleus, a low density of immunoreactive perikarya was detected for NKA or CGRP (Marcos et al., 1998; Marcos et al., 1999). In addition, neurons containing substance P (Han et al., 1996 a) and fibers containing adrenocorticotropin (Rao et al., 1986) have been found in Me.

Lateral nucleus (La)

CGRP or SOM were detected at a low density in fibers in this nucleus, and NPY was present at a moderate density in fibers. Also a moderate density of cell bodies contained NPY, and a low density of perikarya were immunostained for SOM (Marcos et al., 1998; Marcos et al., 1999). Cell bodies and fibers containing PV (Smith et al., 1998) were also observed in La.

COEXISTENCE OF NEUROPEPTIDES IN THE CAT AMYGDALA

Each of the cat amygdaloid nuclei showed cell bodies and/or fibers immunoreactive for several neuropeptides (Table 1). These colocalizations suggest physiological interactions among these neuropeptides in the performance of the amygdaloid complex. The presence of different neuroactive substances in several nuclei also indicates that two or more of these neuroactive substances could coexist in the same neurons and/or fibers.

There are few data about the coexistence of neuropeptides in the cat amygdaloid complex. Smith et al. (Smith et al., 1998) described the presence of PV in some GABAergic cells of the basolateral amygdaloid complex, but this description was carried out in order to study intraamygdaloid inhibitory pathways in the cat.

According on the data published about the distributions of neuropeptides in the amygdaloid complex of the cat (Han et al., 1996 a; Marcos et al., 1998; Marcos et al., 1999; Rao et al., 1986; Siegel et al., 1997;), possible coexistences, based upon morphological criteria, can be suggested in the different nuclei.

AAA:

The dorsal part of this region displayed puncta immunoreactive for SOM, NT, MET-ENK, ACTH or NPY. In addition, NPY and NEO-END could coexist in some short, thin, varicose and branched fibers. In the ventral part of the nucleus, long and unbranched fibers contained NPY and NT. Thus, a possible coexistence of these two neuropeptides may be suggested.

Concerning immunoreactive cell bodies, some round and bipolar neurons were immunostained for SOM or NPY in the AAA.

Table 1.- Summarizes the data available about the distributions of several neuropeptides in the amygdaloid complex of the cat. For abbreviations see the text. F: Fibers; CB: Cell bodies; +: Low density; ++: Moderate density; +++: High density; -: Absence.

TABLE 1	NEO-END		α-MSH		SOM		NKA		NT		LEU-ENK		MET-ENK		NPY		GRP		CGRP		ACTH	
	F	CB	F	CB	F	CB	F	CB	F	CB	F	CB	F	CB	F	CB	F	CB	F	CB	F	CB
AAA	+	-	-	-	++	++	+	-	+	-	-	-	+	-	++	+	-	-	-	-	+	-
Bla	-	-	-	-	++	+	+	-	-	-	-	-	+	-	++	++	-	-	+	-	-	-
Blp	-	-	-	-	++	+	+	-	-	-	-	-	+	-	++	++	-	-	+	-	-	-
Coa	-	-	-	-	++	++	++	-	-	-	-	-	+	-	++	+	++	+	-	+	-	-
Cop	-	-	-	-	++	++	++	-	-	-	-	-	+	-	++	+	++	+	-	+	-	-
BM	-	-	+	-	++	+	+	-	-	-	-	-	-	-	++	+++	-	-	+	-	-	-
Cem	-	-	-	-	+++	-	+	-	++	-	++	+	+	-	+++	++	-	-	+	-	+	-
Cel	-	-	-	-	++	+	-	-	+	-	+	+	+	-	+	++	-	-	+	-	-	-
Me	-	-	-	-	+	-	+	+	-	-	+	-	+	-	++	++	+	++	+	+	+	-
La	-	-	-	-	+	+	-	-	-	-	-	-	-	-	++	++	-	-	+	-	-	-

Bla:

Puncta located at the periphery of the nucleus displayed immunocytochemical staining for SOM, NKA, CGRP or PV. MET-ENK, CGRP or NKA were observed in some short, thin, varicose and unbranched peripheral fibers, and in the whole nucleus SOM or NPY were detected in long, thin and varicose fibers.

In the dorsal part of Bla, from anteriority (A) 14.0 to more rostral levels according to the atlas of Jasper and Ajmone-Marsan (Jasper and Ajmone Marsan, 1966), SOM, NPY or PV were found in neurons displaying similar morphological features: round in shape, medium-sized and with two dendritic processes. These neuropeptides were also observed at caudal levels, but mainly in the periphery of the nucleus, in small and round perikarya. In addition, PV and NPY could also coexist in polygonal cell bodies at caudal levels of the Bla.

Blp:

At the periphery of this nucleus, the pattern of colocalization observed in short, thin, varicose and unbranched fibers was similar to that detected in the Bla. In the same region, puncta showed immunocytochemical staining for NPY, SOM, CGRP, NKA or PV.

The caudal levels of the nucleus, but not the rostral part, displayed the same neuronal profiles as those found in the Bla. Thus, the possible neuropeptide coexistences proposed are the same in both nuclei.

Coa:

Four neuropeptides were detected in puncta: NKA, MET-ENK, NPY and GRP. The dorsal part of the nucleus showed short and varicose fibers immunoreactive for NKA or NPY.

Concerning immunoreactive cell bodies, SOM or CGRP were observed in round, medium-sized perikarya, exhibiting two processes.

Cop:

The pattern of possible coexistence of neuropeptides proposed for this nucleus is the same as that described in Coa.

BM:

The ventral part of the nucleus displayed NKA-, CGRP-, and SOM-immunoreactive puncta. In the dorsal part, NKA or SOM were detected in long, thin and varicose fibers. α-MSH was also present in nerve profiles with these morphological features, but only from A 9.5 to A 11.5. The whole nucleus showed thin, short, varicose and unbranched fibers containing NPY or CGRP.

SOM or NPY were detected in some round, medium-sized perikarya exhibiting two dendritic processes.

Cem:

The highest number of neuropeptides was detected in puncta located in Cem: SOM, NKA, NT, MET-ENK, NPY, CGRP and ACTH. In addition, LEU-ENK, CGRP and NKA were found in short, thin, varicose and unbranched fibers, whereas nerve profiles displaying NPY or NT were short, thin, varicose and branched.

Cel:

The central region of this nucleus showed puncta immunoreactive for SOM, NT, MET-ENK and CGRP. Except for SOM, the same neuropeptides were detected in puncta located at the periphery of the nucleus. In addition, NT, LEU-ENK or NPY were observed in long, thin, varicose and unbranched fibers of the whole nucleus, whereas CGRP or NPY were found in few thin, short, varicose and unbranched nerve profiles.

At the periphery of the nucleus, round, small perikarya, with two dendritic processes, were immunostained for SOM or LEU-ENK.

Me:

In this nucleus, three neuropeptides were observed in puncta: GRP, CGRP, and ACTH. Four others, MET-ENK, LEU-ENK, NKA, and SOM, were detected in short, thin, varicose and unbranched fibers.

Round cell bodies, medium-sized, with two dendritic processes, were observed at A 12.0 in the inner part of the nucleus. These cell bodies contained NPY, NKA, CGRP and GRP. From A 12.5 to more caudal levels, only CGRP and GRP were found in neurons with the same morphology.

La:

The possible coexistence of neuropeptides is proposed only for the ventral aspect of this nucleus. Puncta displayed SOM or CGRP immunostaining, whereas NPY or SOM were detected in short, thin, varicose and unbranched fibers.

Round, small, bipolar cell bodies showed SOM- or PV-immunoreactivity.

The above proposed coexistences of neuropeptides in the different amygdaloid nuclei indicate that double-labeling studies must be performed in the cat amygdala in order to confirm such possible coexistences. These new morphological data could provide better knowledge of the physiological interactions among neuropeptides in the different amygdaloid nuclei.

PEPTIDERGIC PATHWAYS IN THE CAT AMYGDALA

Intra-amygdaloid connections

Efferent projections from the amygdaloid complex to other cerebral targets are under control of

intrinsic amygdaloid circuits. Most studies addressing local circuits in the amygdala of the cat are focused on inhibitory pathways. In general, the major internuclear connections of the amygdala are similar across species, and in rats and cats it has been demonstrated that all intra-amygdaloid connections do not follow a lateromedial course (Pare and Smith, 1998). The evidence suggests that the basal amygdaloid nuclei could transmit information from the La to the Cem, but La does not project to the Cem (Collins and Pare, 1999). The intercalated neurons, clusters of GABAergic cells, are intercalated between the basolateral complex and the central nucleus (Ce). These neurons receive inputs from La and basal nuclei (BM and Bl) and contribute to a massive projection to the Cem (Collins and Pare, 1999), where they may provide a tonic inhibitory input. The basolateral complex also contains a population of GABAergic- and PV-immunoreactive interneurons involved predominantly in feedback inhibition in the nuclei of the basolateral complex (Smith et al., 2000). These interneurons receive massive excitatory inputs (originated in part from the cerebral cortex), and PV-positive terminals are strategically located to exert a powerful inhibitory control over local-circuit amygdaloid neurons (fewer inhibitory inputs) and, in higher amounts, on projection cells (Pare and Smith, 1998; Smith et al., 1998).

Comparing the intra-amygdaloid connections already described in the cat (Pare and Smith, 1998) and the distribution of neuropeptides described above, it can be suggested that NPY could be contained in interneurons, acting as a neuromodulator in some of these intra-amygdaloid connections: for instance, in the projection from the BM nucleus to the La nucleus. In both nuclei, a high or moderate density of NPY-immunoreactive cell bodies and fibers has been observed, suggesting that the NPY-containing neurons of the BM could be interneurons. The same feature for NPY-immunoreactive neurons has been observed in the projection from BM to the Cem. In addition, NPY-positive neurons found in the La may also contribute to modulating the projection described from this nucleus to the Bl. On the other hand, it does not seem possible that SOM-immunoreactive neurons detected in the BM, La and Bl would be peptidergic interneurons on intra-amygdaloid connections.

Possible peptidergic afferences to the cat amygdaloid complex

The origin of the peptidergic fibers observed in the cat amygdala remains to be elucidated, and further studies are needed in order to know in detail the sources of such fibers. However, Me and Cem could receive afferents containing SOM, MET-ENK, LEU-ENK and/or CGRP because in these nuclei only positive fibers, but very scarce cell bodies, or none, have been observed. For the same reason, AAA and Ce might receive NT- and/or NKA- immunoreactive fibers. Following the morphological data available, Coa and Cop could receive afferents containing GRP and/or MET-ENK, and Bl MET-ENK- and/or CGRP-positive afferences. In addition, MET-ENK could be present in fibers reaching AAA, and CGRP in afferents to La, BM and Cop.

The connections of the Ce nucleus of the amygdala have been extensively studied in the cat, particularly those arising from the diencephalon (Volz et al., 1990; Yoshimoto et al., 1989) and from the brainstem (Volz et al., 1990). Comparing the peptidergic distributions detected in these regions of the cat brain with the projections to the Ce amygdaloid nucleus studied (Conti and Sternini, 1989; Coveñas et al., 1990 a; Coveñas et al., 1990 b; Coveñas et al., 2001; Coveñas et al., 2002; De León et al., 1991 a; De León et al., 1991 b; Moss et al., 1983; Velasco et al., 1993), and following the data available on the distribution of neuropeptides in the Cem and Cel nuclei, it is possible to suggest the possible peptidergic sources of some of these projections, as explained in the following section.

Concerning the diencephalon, some thalamic nuclei send projections to the Ce nucleus of the cat amygdala, such as the central medial nucleus and the lateral habenular nucleus (Volz et al., 1990). In the former nucleus, a high density of NT-positive cell bodies has been detected, as well as a low density of neurotensinergic fibers (De León et al., 1991 b). This suggests that the NT-immunoreactive fibers detected in the Ce nucleus of the amygdala could arise from this thalamic nucleus. The same morphological criteria indicate that the NKA-positive fibers observed in the Ce amygdaloid nucleus of the cat might be afferents from the lateral habenular nucleus (Velasco et al., 1993). In addition, other diencephalic projections to the Ce nucleus of the amygdala have been described in the cat, from the anterior hypothalamus and the subparafascicular nucleus (Volz et al., 1990). These projections could be somatostatinergic, since a high density of SOM-positive cell bodies was observed in these two nuclei (De León et al., 1991 a), but no immunoreactive fibers.

Two thalamic nuclei, the parafascicular and the lateral posterior nuclei, could send projections containing NPY to the Ce nucleus of the amygdala (Coveñas et al., 1990 a). The NPY-positive afferences to this nucleus may also arise from some brainstem nuclei, such as the reticular lateral, ambiguus and medial parabrachial (Coveñas et al., 1990 b). However, lesion studies carried out in the rat (Gustafson et al., 1986) indicate that the NPY-positive innervation of the Ce nucleus arising from the brainstem catecholaminergic neurons containing NPY is only a

minor projection to the amygdala of the rat. Thus, as we suggest above, the NPY-immunoreactive neurons detected in the amygdaloid complex could be interneurons whose terminal fields lie within the amygdala, as has also been suggested in rats (Gustafson et al., 1986).

Other brainstem nuclei, namely the dorsal raphe nucleus and the caudal periaqueductal gray matter, project to the Ce nucleus of the cat amygdala (Volz et al., 1990). The distribution of several neuropeptides described in these nuclei suggests that LEU-ENK-positive neurons located in the dorsal raphe nucleus could send efferent projections to the Ce amygdaloid nucleus (Moss et al., 1983) and that CGRP-immunoreactive fibers detected in this nucleus of the cat amygdala might arise from the caudal periaqueductal gray matter (Conti and Sternini, 1989).

Possible peptidergic projecting neurons in the cat amygdala

Following exclusively morphological criteria (a high amount of peptidergic cell bodies and a very low density of fibers, or none), we suggest that the GRP-positive neurons detected in the Me nucleus of the cat amygdala could be projecting neurons. However, the targets of these neurons remain unknown. In the cat, two projecting pathways from the Me have been described. One of them reaches the medial hypothalamus and contains substance P (Shaikh et al., 1993), and the other the tuberomammillary hypothalamic nucleus (Yoshimoto et al., 1989). There are no reports on the distribution of GRP-immunoreactive structures in the cat diencephalon and hence we cannot state that the GRP-positive neurons detected in Me do in fact project to these hypothalamic nuclei.

COMPARATIVE STUDY ON THE DISTRIBUTION OF NEUROPEPTIDES IN THE CAT AMYGDALA

Studies on the mapping and distributions of different neuropeptides have been carried out in the amygdala of mammals, mainly in rats, monkeys, humans and cats. As mentioned above, some neuropeptides were not observed in the cat amygdala by means of immunohistochemical methods, namely LH-RH, END, DYN, γ-MSH, or GAL (Marcos et al., 1998; Marcos et al., 1999). However, these substances were detected in the amygdaloid complex of other mammalian species. Thus, for instance, LH-RH has been found in the central, cortical, medial and lateral nuclei of the rat amygdala (Palkovits, 1988). By means of radioimmunoassay techniques, β-END (1-31) has been detected in the amygdaloid complex of rats and humans (Gramsch et al., 1979; Palkovits, 1988). Concerning the distribution of γ-MSH, no data are available for mammals, but the mapping of pro-opiomelanocortin (POMC) peptides (Khachaturian et al., 1985) in the rat revealed POMC-immunoreactive fibers in all the amygdaloid nuclei. In addition, GAL-positive fibers have been described in the rat amygdala (Melander et al., 1986), as well as DYN A (1-17)- or DYN A (1-13)-immunoreactive profiles (Khachaturian et al., 1982).

These different distribution patterns may be due to species differences (rats or cats), to methodological considerations (radioimmunoassay, immunohistochemistry…), and also to different proteolytic processing of the molecules, as has been suggested in the case of DYN (Marcos et al., 1999). In addition, it is possible that perikarya might synthesize the neuropeptides at a rate too low to allow sufficient buildup for immunohistochemical detection. This could be the case of GAL, as has been previously suggested (see Marcos et al., 1999).

In the present review we compare the distribution of neuropeptides detected in the cat amygdala with their respective distribution patterns in the amygdaloid complex of rats, humans or monkeys.

AAA:

In the cat (Marcos et al., 1998) but not in rats (Matsumoto el al., 1992; Palkovits 1988), two neuropeptides have been observed in fibers of this region: NEO-END and MET-ENK. The opposite pattern has been observed in the case of GRP (Panula et al., 1982), whereas NT displayed a similar distribution in rats (Palkovits, 1988), humans (Benzing et al., 1992) and cats (Marcos et al., 1998), and SOM showed immunoreactive profiles in this region of the squirrel monkey (Desjardins and Parent, 1992), humans (Bouras et al., 1987) and cats (Marcos et al., 1998). In rats (Benoit et al., 1982), radioimmunoassay studies have demonstrated that the highest levels of SOM are detected in the amygdala.

Concerning NPY, in monkeys or humans no NPY-positive profiles were detected in the AAA (McDonald et al., 1995; Walter et al., 1990), and the density of immunoreactive fibers was higher in cats (Marcos et al., 1999) than in rats (Gustafson et al., 1986). In addition, the AAA of the cat showed NPY-immunoreactive puncta and unbranched fibers, whereas these morphologies were not found in the case of rats.

Regarding NKA, the studies carried out in cats constituted the first mapping of this substance in the mammalian amygdala (Marcos et al., 1998). However, studies on the detection of its precursor molecule, pre-pro-tachykinin (PPT) mRNA, allowed workers to describe PPT neurons in the rat AAA (Harlan et al., 1989), whereas no NKA-positive neurons were found in the cat (Marcos et al., 1998).

Bl:

Two neuropeptides have been detected in the fibers of this nucleus in rats, but not in cats. This is the case of GRP (Panula et al., 1982), and α-MSH (Palkovits, 1988). By means of radioimmunoassay techniques, NEO-END was detected in the rat Bl (Palkovits, 1988), and both rats (Palkovits, 1988) and humans (Benzing et al., 1992) displayed NT-positive structures in this region, not observed in the cat (Marcos et al., 1998).

On the other hand, the Bl nuclei displayed MET-ENK-immunoreactive elements in cats, but not in rats (Matsumoto et al., 1992). PPT profiles were not observed in this region of rats (Harlan et al., 1989), whereas NKA-positive fibers were detected in the cat (Marcos et al., 1998). The distribution of CGRP-immunoreactivity was similar in both species (Marcos et al., 1999; Skofitsch and Jacobowitz, 1985).

Concerning SOM, similar distribution patterns have been observed in cats, monkeys and humans (Bouras et al., 1987; Desjardins and Parent, 1992; Marcos et al., 1998). The same feature was found in the case of NPY for these species (Marcos et al., 1999; McDonald et al., 1995; Walter et al., 1990), but the distribution of this neuropeptide was broader in the cat than in the rat (Gustafson et al., 1986), since high densities of both cell bodies and fibers containing NPY were found in the Bla of the cat (Marcos et al., 1999) but not in rats. In addition, the density of NPY-positive fibers was higher in the cat Blp than those detected in the same nucleus of the rat (Gustafson et al., 1986).

Co:

Several neuropeptides were detected in the rat Co nuclei but not in cats: NEO- END (Palkovits, 1988), α-MSH (Palkovits, 1988), and NT (Palkovits, 1988). In the case of NT, immunoreactive profiles were also observed in the Co nuclei of humans (Benzing et al., 1992).

Comparing the distribution of CGRP in rats (Haring et al., 1991; Skofitsch and Jacobowitz, 1985) and cats (Marcos et al., 1999), the results are partially coincident. In both species, CGRP-positive perikarya were detected in Co nuclei, whereas immunoreactive fibers were found only in rats.

In the cat, fibers containing NKA were present in the two Co nuclei (Marcos et al., 1998). In rats, these nuclei displayed PPT neurons (Harlan et al., 1989), whereas in the case of cats no cell bodies were found in these nuclei.

The distribution of GRP- or MET-ENK-immunoreactive elements was similar in the Co nuclei of both cats and rats (Marcos et al., 1999; Matsumoto et al., 1992; Panula et al., 1982), and cats (Marcos et al., 1998), monkeys (Desjardins and Parent, 1992) and humans (Bouras et al., 1987) also displayed a similar distribution pattern of SOM-positive profiles. Concerning NPY, a resemblance can be observed on comparing the results obtained in the Co nuclei of these three species (Marcos et al., 1999; McDonald et al., 1995; Walter et al., 1990). However, the density of NPY-immunoreactive fibers detected in this region was higher in the cat (Marcos et al., 1999) than in the rat (Gustafson et al., 1986).

BM:

The distribution of SOM-positive structures in the BM of cats (Marcos et al., 1998), monkeys and humans (Bouras et al., 1987; Desjardins and Parent, 1992) disclosed a similar pattern. This is also the case of NPY-immunoreactive profiles in cats (Marcos et al., 1999) and humans (Walter et al., 1990), whereas the cat BM nucleus showed a higher density of fibers and cell bodies containing NPY than the rat (Gustafson et al., 1986). In monkeys, the distribution of NPY-positive fibers in this nucleus was similar to that found in the cat, but immunoreactive cell bodies were absent in the monkey (McDonald et al., 1995).

CGRP (Haring et al., 1991; Skofitsch and Jacobowitz, 1985) or α-MSH (Palkovits, 1988) were present in fibers of the BM nucleus of both rats and cats (Marcos et al., 1998; Marcos et al., 1999) in a similar pattern. In two cases, the presence of neuropeptides has been detected in this region in rats but not in cats: GRP (Panula et al., 1982), and NEO-END (Palkovits, 1988). By contrast, NKA-positive fibers were found in cats, whereas no PPT structures were detected in the BM nucleus of the rat (Harlan et al., 1989).

Ce:

In three cases (Palkovits, 1988, Panula et al., 1982) no immunoreactive structures have been detected in the two subdivisions of the Ce nucleus of the amygdala (Cem and Cel) in the cat. However, these neuropeptides displayed positive profiles in the same region of the rat: α-MSH (Palkovits, 1988), GRP (Panula et al., 1982), and NEO-END (Palkovits, 1988). The latter was observed by means of radioimmunoassay techniques as well as by immunofluorescence, showing NEO-END-immunoreactive cell bodies in these nuclei.

The two enkephalinergic peptides studied displayed similar features on comparing their distributions in cats and rats. MET-ENK (Matsumoto et al., 1992) and LEU-ENK (Watson el al., 1982) were detected in fibers of Ce in both species. However, cell bodies containing the respective peptide were only observed in rats, and LEU-ENK-positive perikarya were found exclusively in the Cem division (Watson et al., 1982). In addition, NKA-positive fibers have been detected in the Cem division of the cat (Marcos et al., 1998), although PPT neurons

were observed in both Ce subdivisions of the rat amygdaloid complex (Harlan et al., 1989).

Concerning CGRP-immunoreactive profiles, the two subdivisions of Ce showed fibers containing the peptide in both rats (Haring et al., 1991; Skofitsch and Jacobowitz, 1985) and cats (Marcos et al., 1999). In the latter, no CGRP-positive cell bodies were found, but in rats Cel showed perikarya containing this neuropeptide (Haring et al., 1991).

Neurotensinergic elements were distributed in a similar pattern in the Ce of cats (Marcos et al., 1998), rats (Palkovits, 1988) and humans (Benzing et al., 1992). The same has been observed for the distribution of SOM-immunoreactive fibers in this region of cats (Marcos et al., 1998), monkeys (Desjardins and Parent, 1992) and humans (Bouras et al., 1987). However, cell bodies containing SOM were found in cats only in Cel (Marcos et al., 1998), whereas both subdivisions of the Ce displayed SOM-positive perikarya in humans (Bouras et al., 1987).

A different distribution pattern of NPY-immunoreactive cell bodies has also been detected in these nuclei. In cats (Marcos et al., 1999) and monkeys (McDonald et al., 1995), perikarya containing this neuropeptide were observed in both subdivisions of Ce, but humans lack labelled cell bodies in Cem (Walter et al., 1990). In addition, this subdivision showed a higher amount of NPY-positive cell bodies in the cat (Marcos et al., 1999) than in rats (Gustafson et al., 1986).

Me:

The presence of several neuropeptides has been described in this region of the rat, but not in cats (Marcos et al., 1998; Marcos et al., 1999): NEO-END, α-MSH and NT (Palkovits, 1988). In this latter, the human Me also displayed immunoreactive profiles (Benzing et al., 1992). The opposite distribution in cats and rats has been observed for LEU-ENK-positive fibers (Watson et al., 1982) and for cell bodies containing GRP, although both species showed GRP-immunoreactive fibers in this region (Panula et al., 1982).

A similar distribution pattern was found in the Me of cats and rats for MET-ENK-positive fibers (Matsumoto et al., 1992) and CGRP-labelled cell bodies and fibers (Haring et al., 1991; Skofitsch and Jacobowitz, 1985). This nucleus is the only one showing NKA-immunoreactive cell bodies in the cat (Marcos et al., 1998) and PPT neurons in the rat (Harlan et al., 1989).

The distribution of somatostatinergic profiles was similar in the Me nucleus of the cat (Marcos et al., 1998), the human (Bouras et al., 1987) and the monkey (Desjardins and Parent, 1992). Both cats (Marcos et al., 1999) and humans (Walter et al., 1990) also displayed a similar distribution of NPY-containing structures in this region, whereas in the monkey (McDonald et al., 1995) no NPY-immunoreactive cell bodies have been detected in Me. It is in the rat amygdaloid nucleus that the highest amount of NPY-positive cell bodies and fibers has been found (Gustafson et al., 1986), whereas in the cat only moderate densities of these elements can be observed (Marcos et al., 1999), and at caudal levels, no cell bodies containing NPY were detected.

La:

In general, this amygdaloid nucleus seems to have a more restricted distribution of neuropeptides in the cat than in the rat. Thus, positive profiles for NEO-END (Palkovits, 1988), GRP (Panula et al., 1982), NT (Palkovits, 1988) or PPT (Harlan et al., 1989), the molecule precursor of NKA, have been detected in the La nucleus of the rat but not in the cat (Marcos et al., 1998; Marcos et al., 1999). In humans, NT-immunoreactive elements were also observed in this region (Benzing et al., 1992).

However, CGRP-containing fibers have been detected in cats (Marcos et al., 1999), but not in rats (Haring et al., 1991; Skofitsch and Jacobowitz, 1985).

On the other hand, SOM (Bouras et al., 1987; Desjardins and Parent, 1992; Marcos et al., 1998) and NPY (Marcos et al., 1999; McDonald et al., 1995; Walter et al., 1990) displayed a similar distribution pattern in the La amygdaloid nucleus of cats, monkeys and humans. On comparing cats and rats, caudo-rostral differences have been detected in the mapping of NPY-positive cell bodies. At caudal levels, a higher density of these perikarya was observed in cats, whereas the rat showed a greater number of cell bodies containing NPY at the rostral levels of the La nucleus (Gustafson et al., 1986).

POSSIBLE PHYSIOLOGICAL FUNCTIONS OF NEUROPEPTIDES IN THE CAT AMYGDALA

The use of immunohistochemical techniques for different neuropeptides in the cat amygdaloid complex (Marcos et al., 1998; Marcos et al., 1999) has disclosed a broad variety in staining patterns. This variety of patterns, in addition to the many functions in which the amygdala has been implicated, enhances the difficulty of assigning particular roles to the neuropeptides studied. In addition, the co-localization of several neuropeptides in the same amygdaloid nucleus suggests that such neuropeptides could have interactions among them, and possibly exert a complicated control as neuromodulators of the different physiological functions in which the amygdala is involved.

These mechanisms range from associative memory and learning to emotional states and

visceral reactions (De Olmos, 1990). In the cat, defensive rage behavior is a widely studied emotional mechanism (Shaikh and Siegel, 1994; Siegel and Schubert, 1995; Siegel et al., 1997). It has been established that several amygdaloid regions powerfully modulate this behavior: the medial nucleus and the basal complex facilitate defensive rage, and the central nucleus suppresses it (Shaikh and Siegel, 1994). In addition, the medial hypothalamus and midbrain periaqueductal gray are the most important structures mediating defensive rage behavior, whereas the perifornical lateral hypothalamus clearly mediates predatory attack behavior (Gregg and Siegel, 2001). As has been detailed in a previous section of this paper (see "Peptidergic pathways in the cat amygdala"), the amygdaloid complex and these areas are connected, and we have suggested that some of the neuropeptides studied could participate in some way in such connections, perhaps by modulating the intensity of attack and rage. This is in agreement with a previous study that revealed that several neurotransmitters facilitate defensive rage within the medial hypothalamus and the periaqueductal gray (such as glutamate, substance P and cholecystokinin), and that opioid peptides suppress it (Gregg and Siegel, 2001). Thus, it seems likely that one or more of the neuropeptides studied (Marcos et al., 1998; Marcos et al., 1999) could also be involved in the modulation of the facilitation and/or suppression of these behavioral mechanisms.

Auditory fear conditioning is a mechanism that is also related to the amygdaloid complex, and it is known that the La nucleus is the input station for auditory conditioned stimuli, and that Cem is the output for conditioned fear responses (Pare and Collins, 2000). As described in a previous section (see "Peptidergic pathways in the cat amygdala"), the main intra-amygdaloid targets of the La are the BM and the Bl nuclei, which in turn project to the Cem. It seems likely that the BM and Bl nuclei contribute to the transmission of auditory conditioned stimuli to the Cem in auditory fear conditioning (Pare et al., 1995). Thus, the neuropeptides detected in these regions of the cat amygdala could play a modulatory role in such intra-amygdaloid connections.

Future research on neuropeptides in the cat amygdala

The present and previous papers (Conti and Sternini, 1989; Coveñas et al., 1990a; Coveñas et al., 1990b; Coveñas et al., 2001; Coveñas et al., 2002; De León et al., 1991a; De León et al., 1991b; Gregg and Siegel, 2001; Han et al., 1996a; Han et al., Marcos et al., 1998; Marcos et al., 1999; 1996b; Moss et al., 1983; Rao et al., 1986; Shaikh and Siegel, 1994; Shaikh et al., 1993; Siegel and Schubert, 1995; Siegel et al., 1997; Smith et al., 1998; Smith et al., 2000; Velasco et al., 1993) indicate that study of the distribution of neuropeptides in the cat brain has increased considerably in the last two decades, as has our knowledge of the physiological functions that such neuropeptides carry out in the regions where they are located. However, many other studies remain to be carried out, and it seems clear that a complete mapping of more neuropeptides should be performed in the areas partially studied in the cat brain (i. e., thalamus, hypothalamus, amygdala, brainstem, etc.) as well as in other regions hitherto not analysed in the cat (i.e., cerebral cortex).

Moreover, the co-localization of several neuropeptides in the same amygdaloid nucleus suggests possible co-existences of these neuropeptides in the same fibers and/or cell bodies. Thus, double immunohistochemical studies may be carried out in order to confirm these possible co-existences. These immunohistochemical studies might be completed by *in situ hybridization* techniques, which will contribute to a better knowledge of all the morphologic aspects of peptide distribution in the cat amygdala.

In addition, immunohistochemistry could be performed together with tracing studies in order to know the peptidergic content of both intra- and extra-amygdaloid connections. This kind of study will also allow workers to detect the sources of peptidergic afferents reaching the amygdaloid nuclei.

Finally, analysis of the distribution of different neuropeptide receptors as well as knowledge of the peptidergic synaptic connections, together with the above-mentioned techniques and others, are required in order to determine the distribution and the physiological functions of neuropeptides in the amygdaloid complex of the cat.

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Abbreviations

AAA: anterior amygdaloid area

Bla: anterior division of the basolateral nucleus of the amygdala

Blp: posterior division of the basolateral nucleus of the amygdala

BM: basomedial nucleus of the amygdala

Cel: lateral part of the central nucleus of the amygdala

Cem: medial part of the central nucleus of the amygdala
Coa: anterior cortical nucleus of the amygdala
La: lateral nucleus of the amygdala
Me: medial nucleus of the amygdala

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