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Topographic Organization of Connections Between the Hypothalamus and Prefrontal Cortex in the Rhesus Monkey

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ABSTRACT

Prefrontal cortices have been implicated in autonomic function, but their role in this activity is not well understood. Orbital and medial prefrontal cortices receive input from cortical and subcortical structures associated with emotions. Thus, the prefrontal cortex may be an essential link for autonomic responses driven by emotions. Classic studies have demonstrated the existence of projections between prefrontal cortex and the hypothalamus, a central autonomic structure, but the topographic organization of these connections in the monkey has not been clearly established. We investigated the organization of bidirectional connections between these areas in the rhesus monkey by using tracer injections in orbital, medial, and lateral prefrontal areas. All prefrontal areas investigated received projections from the hypothalamus, originating mainly in the posterior hypothalamus. Differences in the topography of hypothalamic projection neurons were related to both the location and type of the target cortical area. Injections in lateral eulaminate prefrontal areas primarily labeled neurons in the posterior hypothalamus that were equally distributed in the lateral and medial hypothalamus. In contrast, injections in orbitofrontal and medial limbic cortices labeled neurons in the anterior and tuberal regions of the hypothalamus and in the posterior region. Projection neurons targeting orbital limbic cortices were more prevalent in the lateral part of the hypothalamus, whereas those targeting medial limbic cortices were more prevalent in the medial hypothalamus. In comparison to the ascending projections, descending projections from prefrontal cortex to the hypothalamus were highly specific, originating mostly from orbital and medial prefrontal cortices. The ascending and descending connections overlapped in the hypothalamus in areas that have autonomic functions. These results suggest that specific orbitofrontal and medial prefrontal areas exert a direct influence on the hypothalamus and may be important for the autonomic responses evoked by complex emotional situations. J. Comp. Neurol. 398:393–419, 1998.

Indexing terms: limbic; autonomic; orbitofrontal; emotion; medial prefrontal

Strong emotions often elicit activation of the autonomic nervous system, which causes changes in blood pressure and respiration. Prefrontal cortices have been implicated in emotional function (for reviews, see Damasio, 1994; Barbas, 1995b) and receive input from areas associated with emotion, including the amygdala, thalamic limbic nuclei, and cingulate cortex (Price and Amaral, 1981; Amaral, 1985; Davis, 1992; Heilig et al., 1994; for reviews, see Vogt et al., 1992; Barbas, 1995b). In addition, prefrontal areas have connections with autonomic structures and long have been associated with autonomic functions. Classic studies have demonstrated that electrical stimulation of prefrontal limbic cortices causes respiratory arrest and significantly increased blood pressure in primates (Bailey and Sweet, 1940; Smith, 1945; Ward, 1948; Kaada et al., 1949). The evoked autonomic responses are strong enough to cause cardiac ischemia and myocardial infarction (Cropp and Manning, 1960; Hall et al., 1977; Hall and Cornish, 1977). More recent evidence supports the idea that prefrontal limbic cortices are important for autonomic responses to emotions (Damasio et al., 1990; Bechara et al., 1996; Powell et al., 1996). Because the hypothalamus is a critical component of the central autonomic nervous system, its

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connections with prefrontal cortices may be involved in autonomic function.

Ascending and descending connections between the hypothalamus and prefrontal cortices may be involved in the evaluation of emotional stimuli and in the autonomic responses elicited by such stimuli. Hypothalamic connections with cortical areas probably provide a pathway for feedback from the hypothalamus about the state of the body and have been shown to be important in arousal (Lin et al., 1988). Prefrontal projections to the hypothalamus may be part of a descending pathway necessary for complex cognitive and emotional states to elicit physical changes (Damasio, 1994) such as those associated with embarrassment or jealousy.

There is evidence from studies in rats and monkeys that projections from the hypothalamus innervate the entire cortical mantle, including prefrontal areas (Kievit and Kuypers, 1975; McKinney et al., 1983; Mesulam et al., 1983; Tigges et al., 1983; Vincent et al., 1983; Köhler and Swanson, 1984; Saper, 1985). Previous studies in the monkey indicated that projection neurons to the cortex originate in the lateral and dorsal parts of the hypothalamus, particularly in its posterior extent (Kievit and Kuypers, 1975; Jacobson et al., 1978; Potter and Nauta, 1979; Mizuno et al., 1982; Tigges et al., 1982; Mesulam et al., 1983; Tigges et al., 1983; Morecraft et al., 1992).

The projections from the hypothalamus to cortex have been described as diffuse or nonspecific (Mesulam et al., 1983; Vincent et al., 1983). In their widespread distribution, hypothalamic projections may resemble the ascending projections from the basal forebrain or regions of the brainstem, including the noradrenergic projections from the locus coeruleus and the serotonergic projections of the raphe nuclei (for review, see Foote and Morrison, 1987). Diffuse projections are not necessarily transmitter specific. The thalamus also has diffuse projections to the cortex and specific projections from some nuclei to particular cortical areas (for review, see Jones, 1985). Both patterns are apparent in the thalamic projections to prefrontal areas (Jones and Leavitt, 1974; Kievit and Kuypers, 1977; Potter and Nauta, 1979; Goldman-Rakic and Porrino, 1985; Ilinsky et al., 1985; Barbas et al., 1991; Dermon and Barbas, 1994). Other areas, including the amygdala and the hippocampus, have relatively specific patterns of projection to the prefrontal cortex (Rosene and Van Hoesen, 1977; Porrino et al., 1981; Amaral and Price, 1984; Barbas and De Olmos, 1990; Barbas and Blatt, 1995). The amygdala projects most strongly to the orbitofrontal areas, whereas the hippocampal projections are directed preferentially to medial prefrontal cortices (for review, see Barbas, 1997). It is possible that there are specific as well as nonspecific hypothalamic projections to the cortex, as observed in the thalamus. In the rat, although hypothalamic cell groups project diffusely to the cortex, they nevertheless show some degree of topography (Saper, 1985).

Much less is known about the descending projections from prefrontal areas to the hypothalamus than the ascending projections. In the rat, cortical inputs to the hypothalamus originate primarily in the infralimbic, prelimbic, insular, and lateral frontal areas (Kita and Oomura, 1982; Hurley et al., 1991; Yasui et al., 1991; Buchanan et al., 1994). In the monkey, evidence derived mostly from classic studies indicates that the prefrontal cortex provides direct input to the hypothalamus (Wall et al., 1951; Nauta, 1962; DeVito and Smith, 1964; Johnson et al., 1968; Nauta and Haymaker, 1969; Tazawa et al., 1987; Öngür et al., 1996).

The topographic organization of connections between prefrontal areas and the hypothalamus in the monkey has received little attention, although detailed studies have been carried out in rats (Divac et al., 1978; Kita and Oomura, 1982; Saper, 1985; Ericson et al., 1991; Hurley et al., 1991; Canteras et al., 1994; Vertes et al., 1995). In this study, we investigated the organization of descending and ascending connections between the hypothalamus and prefrontal cortex in the rhesus monkey. We wanted to know which areas of the hypothalamus project to prefrontal cortex: Does the hypothalamus project to prefrontal cortex in a diffuse or nonspecific manner, or are there differences in the number or topography of hypothalamic neurons projecting to regionally specific prefrontal areas? We also wanted to determine which prefrontal areas issue projections to the hypothalamus, and where do such descending projections terminate? Do projections origi-

Abbreviations

A	arcuate sulcus
AA	anterior hypothalamic area
An	anterior hypothalamic nucleus
C	central sulcus
CC	corpus callosum
Cg	cingulate gyrus
cp	cerebral peduncle
DA	dorsal hypothalamic area
Dm	dorsomedial nucleus
f	fornix
FF	field of Forel
GP	globus pallidus
ic	internal capsule
In	infundibular nucleus
Inf	infundibulum
LA	lateral hypothalamic area
LF	lateral fissure
LM	lateral mammillary nucleus
LO	lateral orbital sulcus
LT	lateral tuberal nucleus
MM	medial mammillary nucleus
MO	medial orbital sulcus
mt	mammillothalamic tract
oc	optic chiasm
OLF	olfactory area
ot	optic tract
P	principal sulcus
PA	posterior hypothalamic area
Pa	paraventricular nucleus
PAll	periallocortex
Pef	perifornical nucleus
PeM	perimammillary nucleus
Pir	prepiriform cortex
PM	paramammillary nucleus
Pro	proisocortex
Ro	rostral sulcus
Sc	suprachiasmatic nucleus
SI	substantia innominata
SM	supramammillary nucleus
SN	substantia nigra
Soa	supraoptic nucleus, anterior
Sot	supraoptic nucleus, tuberal
ST	superior temporal sulcus
STh	subthalamic nucleus
TCA	area of the tuber cinereum
TM	tuberomammillary nucleus
Vm	ventromedial nucleus
ZI	zona incerta

nate and terminate in autonomic areas of the hypothalamus? Are the connections reciprocal, or are there prefrontal areas that receive input from the hypothalamus but do not send input to it? In previous studies, we had noted differences in the connections of various brain structures with prefrontal cortices associated with the laminar features of the target prefrontal area (for review, see Barbas, 1995b). Similarly, in the present study, we investigated whether the connections of the hypothalamus are different with limbic prefrontal cortices compared with the structurally distinct eulaminate prefrontal cortices.

MATERIALS AND METHODS

Experiments were conducted on 24 rhesus monkeys (*Macaca mulatta*) according to the Guide for Care and Use of Laboratory Animals (DHEW Publication no. [NIH] 80–22, revised 1987, Office of Science and Health Reports, DRR/NIH, Bethesda, MD). The animals were anesthetized intramuscularly with ketamine hydrochloride (10 mg/kg) followed by sodium pentobarbital, administered intravenously through a femoral catheter until a surgical level of anesthesia was achieved. Additional anesthetic was administered during surgery as needed. Surgery was performed under aseptic conditions. The monkey's head was firmly positioned in a holder that left the cranium unobstructed for surgical approach. A bone defect was made, the dura was retracted, and the cortex was exposed.

Surgical and histological procedures

Injections of horseradish peroxidase conjugated to wheat germ agglutinin (HRP-WGA; Sigma, St. Louis, MO) were placed in prefrontal cortices or adjacent premotor cortices in 17 animals; fluorescent dyes (fast blue, diamidino yellow) were injected in 3 animals; and ^{3}H-labeled amino acids were placed in 4 animals. All injections were made by using a microsyringe (Hamilton, 5 µl) mounted on a microdrive. The needle was lowered to the desired site under microscopic guidance. In each case, small amounts (0.05–0.1 µl of 8% HRP-WGA; 0.4 µl of 3% fast blue or diamidino yellow; 0.4–1.0 µl of [^{3}H]leucine and [^{3}H]proline, specific activity 40–80 µCi) of the tracer were delivered 1.5 mm below the pial surface at each of two adjacent sites (separated by 1–2 mm) over a 30-minute period. In cases with fluorescent dyes, two or more different sites can be injected in each animal. The total number of cortical sites examined was 26. Eight injections were in orbital prefrontal areas, eight in medial areas, eight in lateral prefrontal areas, and two in lateral premotor cortices situated adjacent to prefrontal areas.

In the HRP experiments, the monkeys were anesthetized deeply 40–48 hours after injection and perfused through the heart with saline followed by 2 liters of fixative (1.25% glutaraldehyde, 1% paraformaldehyde in 0.1 M phosphate buffer at pH 7.4), followed by 2 liters of cold (4°C) phosphate buffer (0.1 M, pH 7.4). The brain was removed from the skull, photographed, and placed in glycerol phosphate buffer (10% glycerol and 2% dimethyl sulfoxide [DMSO] in 0.1 M phosphate buffer at pH 7.4) for 1 day and then in 20% glycerol phosphate buffer for another 2 days. The brain was then frozen in –75°C isopentane, transferred to a freezing microtome, and cut in the coronal plane at 40 µm in 10 series. One series of sections was treated to visualize HRP (Mesulam et al., 1980). The tissue was mounted, dried, and counterstained with neutral red.

In animals injected with fluorescent dyes, the survival period was 10–14 days. The animals were anesthetized deeply and perfused with 6% paraformaldehyde in 0.1 M cacodylate buffer (pH 7.4). The brain was postfixed in a solution of 6% paraformaldehyde with glycerol and 2% DMSO, frozen, and cut as described above. Three adjacent series of sections were saved for microscopic analysis. These series were mounted and dried onto gelatin-coated slides. The three series were stored in light-tight boxes with Drierite at 4°C. Seven days later, the first series was coverslipped with Fluoromount and returned to dark storage at 4°C. The second series, left without a coverslip, was used to chart the location of retrogradely labeled neurons. After the second series was charted, it was stained with cresyl violet, covered with a coverslip, and used to determine the cytoarchitectonic boundaries.

The animals injected with ^{3}H-labeled amino acids were anesthetized deeply and perfused with 10% Formalin after a 10-day survival period. The brain was embedded in paraffin, cut in 10-µm coronal sections, and mounted on glass slides. Sections were processed according to the autoradiographic method of Cowan et al. (1972), counterstained with thionin, and covered with a coverslip.

Series of sections adjacent to those prepared to visualize HRP or fluorescent dyes were stained for Nissl bodies, myelin, and acetylcholinesterase (AChE) to aid in delineating architectonic borders (Geneser-Jensen and Blackstad, 1971; Gallyas, 1979). Brains from three additional animals were used to examine the differential distribution of three neurochemical markers (NADPH diaphorase [a marker for localizing nitric oxide synthase] and phosphoproteins Inhibitor-1 and DARPP-32) in the various hypothalamic nuclei and areas. These markers are useful because they have different patterns of distribution in various limbic areas (Gustafson et al., 1991; Barbas et al., 1993; Dombrowski and Barbas, 1996). The borders identified in matched series were placed on the charted drawings with the labeled neurons and also marked on images captured with a charge-coupled device (CCD; Dag-MTI, Michigan City, IN) camera by using blood vessels as landmarks.

Data analysis

Mapping projection neurons. Brain sections, prepared according to the methods described above, were viewed microscopically under brightfield and darkfield illumination. Hypothalamic drawings, the locations of retrogradely labeled neurons, and the sites of blood vessels used as landmarks were transferred from the slides onto paper by means of a digital plotter (Hewlett Packard, 7475A) electronically coupled to the stage of the microscope and to a computer (Austin 486). In this system, the analog signals are converted to digital signals via an analog-to-digital converter (Data Translation, Marlboro, MA) in the computer. Software developed for this purpose ensured that each labeled neuron noted by the experimenter was recorded only once, as described previously (Barbas and De Olmos, 1990). Movement of the microscope stage was recorded via linear potentiometers (Vernitech, Axsys, San Diego, CA) mounted on the X and Y axes of the stage of the microscope and coupled to a power supply. This procedure allowed accurate topographic presentation of labeled neurons within the hypothalamus.

All of the prepared sections through the hypothalamus in one series were examined and charted. Labeled neurons were counted by outlining the area of interest (e.g., one nucleus) by moving the X and Y axes of the stage of the microscope. The number of labeled neurons within the enclosed area was calculated by an algorithm written for this purpose.

Because many hypothalamic nuclei are small, it was necessary to match the rostrocaudal level of sections across cases as much as possible to ensure equivalent opportunity to sample from each nucleus or area. The interval between sections was 400 μm (every 10th section cut at 40 μm), so that a hypothalamic area only 500 μm in the rostrocaudal dimension could appear in either one or two sections. If this area appeared in two sections, it might appear to have twice as many retrogradely labeled neurons than when represented in a single section. To prevent this distortion, the same number of sections (19) at approximately the same rostrocaudal level of the hypothalamus were included in the final analysis for the HRP experiments (mean number of sections through the hypothalamus = 18.9). Nineteen sections at intervals of 300–480 μm were selected from the atlas of Bleier (1984) to use to match sections from the HRP cases. For rostrocaudal levels not represented by a section for an individual case, the number of labeled neurons per region was interpolated from those plotted in adjacent sections. Similarly, sections at rostrocaudal levels that fell between the appropriate levels were excluded from the final analysis. This procedure corrected for individual variation in length of the hypothalamus and was important for accurate comparison of the rostrocaudal distribution of labeled neurons between cases. The cases with fluorescent dye injections did not have every section plotted through the hypothalamus and thus were not included in the quantitative analysis of retrogradely labeled neurons. These cases were used to address questions about topography of projections. Statistical comparisons were made using Student's t-test.

Mapping anterograde label. For cases with HRP or ^{3}H-labeled amino acid injections, the density and distribution of anterograde label in the hypothalamus were determined by using an image analysis system (MetaMorph, Universal Imaging System Corp., West Chester, PA). This high-resolution system uses a CCD camera mounted on the microscope to capture images directly from brain sections. All measurements were made under darkfield illumination at 100× magnification. An initial density measure in each section was taken in an adjacent area with no anterograde label to determine the level of background density. The illumination and camera were adjusted to minimize slight differences in tissue reflectance from area to area, and thus background levels were consistent across areas measured. The background density was subtracted from subsequent density measures to determine whether labeling was above background level. Measurements of density were taken from multiple sample squares distributed throughout each area or nucleus to avoid retrogradely labeled neurons or small artifacts. Density measurements were converted to a scale of light anterograde label (density score = 1–20), moderate anterograde label (density score = 21–80), or dense anterograde label (density score > 80), which correlated closely with independent visual analyses of these areas using a 0–3 rating method (0 = no label, 1 = light, 2 = moderate, 3 = dense; Pearson r = 0.94, $P < 0.001$).

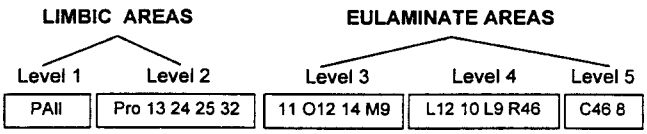


Fig. 1. Structural levels of prefrontal cortical areas based on their degree of laminar definition (Barbas and Rempel-Clower, 1997). Level 1: Agranular limbic areas. Level 2: Dysgranular limbic areas. Levels 3–5: Eulaminate areas. Letters appearing before architectonic areas are for lateral (L), medial (M), orbital (O), rostral (R), and caudal (C).

Reconstruction of injection sites

The cortical regions containing the injection sites were reconstructed serially by using the sulci as landmarks, as described previously (Barbas, 1988), and are shown on diagrams of the surface of the cortex. The latter were drawn from photographs of each brain showing the external morphology of the experimental hemispheres. References to architectonic areas of the prefrontal cortex are according to a previous study (Barbas and Pandya, 1989).

Designation of cortical levels

Prefrontal cortex is a heterogeneous region that includes different kinds of cortices with different structural characteristics. Limbic cortices have three or four layers and either lack or have a poorly developed granular layer IV. In contrast, eulaminate areas have six layers and better laminar definition. In previous studies, we had noted marked differences in the connections of prefrontal cortices with cortical and subcortical structures based on the laminar features of the prefrontal target areas (Dermon and Barbas, 1994; Barbas and Rempel-Clower, 1997; for review, see Barbas, 1995b). To test whether the hypothalamic connections also varied for different types of cortices, prefrontal areas were grouped according to the degree of their laminar definition and assigned a rating of 1–5 (Fig. 1), as described previously (Barbas and Rempel-Clower, 1997). The agranular limbic areas (periallocortex [PAll]), which have only three distinguishable layers, were placed in level 1. Adjacent dysgranular limbic areas (e.g. proisocortex [Pro] and areas 25 and 32), which have four distinguishable layers, were placed in level 2. The six-layered eulaminate areas were placed in levels 3–5 according to their degree of laminar distinction. Eulaminate areas located farthest from limbic cortices have the most distinct lamination, including a wide granular layer IV, and were placed in level 5 (area 8 and caudal area 46). Eulaminate cortices adjacent to limbic cortices have six layers, but the width of layer IV and their laminar distinction are lower than in other eulaminate areas, so these cortices were placed in level 3 (e.g. area 11, orbital area 12, and medial area 9). Level 4 cortices are eulaminate cortices situated between levels 3 and 5 that have an intermediate laminar definition (e.g., dorsal area 10).

RESULTS

Hypothalamic borders

Systematic studies have been done in the rat to classify hypothalamic neural groups according to both neurochemistry and connections. Because similar systematic studies remain to be done in the monkey, the nomenclature and divisions of the hypothalamus are based on limited knowl-

TABLE 1. Summary of Terminology for the Tuberal and Posterior Hypothalamus

Area/ nucleus	Alternative name/subdivisions	Cytoarchitectural and neurochemical characteristics[1]	Sp.[2]	Reference[3]
Tuberal hypothalamus				
Lateral division				
LA		Diverse cell types; AChE (S, VAC); MCH (B et al.); histamine (MWU)	h m r	NH, S MWU, VAC B et al.
TM	Magnocellular tuberomammillary n. (Bl, MWU); lateral tuberal n. (G et al.); n. of the ansa lenticularis (PA)	Large, intensely stained cells; histamine (MWU); GluR2/3 (G et al.)	h, r m	S, S85 Bl, MWU, G et al., PA
	Tuberomammillary complex (Br)	Large cells, densely stained Nissl material is preferentially concentrated at periphery of soma, lipofuscin granules are clustered[4]	h h, m	BB, Br, L, NH M
	Subdivisions[5]: TMv, TMdm, TMdif (K et al.); TMVc, TMVr, TMMv, TMMd, TMdif (E et al.); E1–E5 (I et al.)	GAD, substance P (K et al.); histidine decarboxylase (E et al., I et al.); galanin, adenosine deaminase (S et al.)	r	K et al., E et al., I et al., S et al.
LT	Tuberal n. (Bl) and tuberomammillary n. (Bl,[6] VAC, G et al.)	Clusters of small, medium-stained cells embedded in a gelatinous appearing matrix; GluR2/3 (G et al.)	h m	BB, NH, M, S Bl, G et al., PA, VAC
Medial division				
TCA	Retrochiasmatic area (SK), retrochiasmatic n. (BB)	Heterogeneous cell types	h r	BB SK
Vm		GluR1 and GluR2/3 (G et al.)	h m	NH, S G et al., PA
Dm		GluR1 and GluR2/3 (G et al.)	h m	NH, S G et al., PA
DA	Dorsal hypothalamic n. (NH)	Histamine (MWU)	h m	NH, I MWU
In	Arcuate n. (S)	Tightly packed cells	h	BB, NH, S
Posterior hypothalamus				
Lateral division				
LA		(See description for tuberal LA, but not immunoreactive for MCH)		
PM	N. intercalatus (L)	Large, deeply stained, multipolar cells; AChE (VAC); GluR1 and GluR2/3 (G et al.); histamine (MWU)	h m	L G et al. MWU, VAC
Medial division				
PA	Posterior hypothalamic n. (NH, VAC)	Heterogeneous cell group, most medium-sized & multipolar; AChE (VAC); histamine (MWU)	h m	NH, S MWU, VAC
Pef		Large cells; AChE (VAC); histamine (MWU); GluR1 and GluR2/3 (G et al.)	m	G et al., MWU, VAC
MM		Medium-sized multipolar cells with moderately dense Nissl substance	h	NH, S
LM	N. intercalatus (NH)	Large, darkly staining, polygonal cells; AChE (VAC)	h m	NH, S VAC
PeM	Lateral mammillary n. (NH)	GluR2/3 (G et al.); histamine (MWU)	h m	NH G et al., MWU
SM		Small, isomorphous cells; AChE in plexus, not in cells (VAC)	h m	NH VAC

[1]Some or all cells in each area/nucleus were positive for the neurochemicals listed.
[2]Sp., species; h, human; m, monkey; r, rat.
[3]Reference abbreviations: B et al., Bittencourt et al., 1992; BB, Braak and Braak, 1992; Bl, Bleier, 1984; Br, Brockhaus, 1942; E et al., Ericson et al., 1987; G et al., Ginsberg et al., 1995; I, Ingram, 1940; I et al., Inagaki et al., 1990; K et al., Köhler et al., 1985; L, Le Gros Clark, 1936; M, Malone, 1914; MWU, Manning et al., 1996; NH, Nauta and Haymaker, 1969; PA, Papez and Aronson, 1934; S, Saper, 1990; S85, Saper, 1985; S et al., Staines et al., 1986; SK, Swanson and Kuypers, 1980; VAC, Veazey et al., 1982.
[4]The more broadly defined tuberomammillary nucleus includes scattered large neurons in the lateral hypothalamus, surrounding LT and MM, and surrounding the fornix.
[5]Areas identified neurochemically as the tuberomammillary nucleus have been subdivided in the rat into (1) a ventral portion, TMv, divided into caudal (TMVc, E1) and rostral (TMVr, E2) parts; (2) a medial portion, TMdm, divided into ventral (TMMv, E3) and dorsal (TMMd, E4) parts; and (3) a diffuse portion (TMdif, E5).
[6]The LT clusters are called the tuberal nucleus, located more anteriorly, and the tuberomammillary nucleus according to the atlas of Bleier (1984).
Abbreviations: AChE, acetylcholinesterase; GAD, glutamic acid decarboxylase; GluR1 and GluR2/3, AMPA receptor subunits; MCH, melanin-concentrating hormone; n., nucleus.

edge of its connections and neurochemical characteristics. The terminology for the hypothalamus in the monkey—particularly its posterior half—contains many discrepancies in the literature. We have constructed a table that summarizes some of the terminology used by different investigators for reference (Table 1). This table includes only some of the alternate terms and definitions for the tuberal and posterior hypothalamus from previous studies in the human and monkey as well as a few particularly relevant studies in the rat; it is not comprehensive. Table 1 is intended to facilitate comparison between previous studies and the findings presented here. The terminology used in the present study relies on a combination of the classic and modern studies in the human and monkey (Malone, 1914; Le Gros Clark, 1936; Nauta and Haymaker, 1969; Veazey et al., 1982; Saper, 1990), including work in primates delineating the neurochemical characteristics of these areas (Ginsberg et al., 1995; Manning et al., 1996).

The hypothalamus can be divided rostrocaudally into the preoptic, anterior, tuberal, and posterior regions as well as into periventricular, medial, and lateral zones along the mediolateral dimension (Nauta and Haymaker, 1969; Saper, 1990). Most of the clearly defined cell groups within the hypothalamus have been identified as nuclei and are within the medial zone. The medial and periventricular zones make up the medial division described here. The lateral division generally is less cellular than the medial division and contains the fiber bundles that pass through the hypothalamus. Loosely arranged cells surrounding defined nuclei are called areas and are named according to their topographic position in the hypothalamus (e.g., dorsal hypothalamic area [DA], lateral hypothalamic area [LA]). Regional designation of a particular

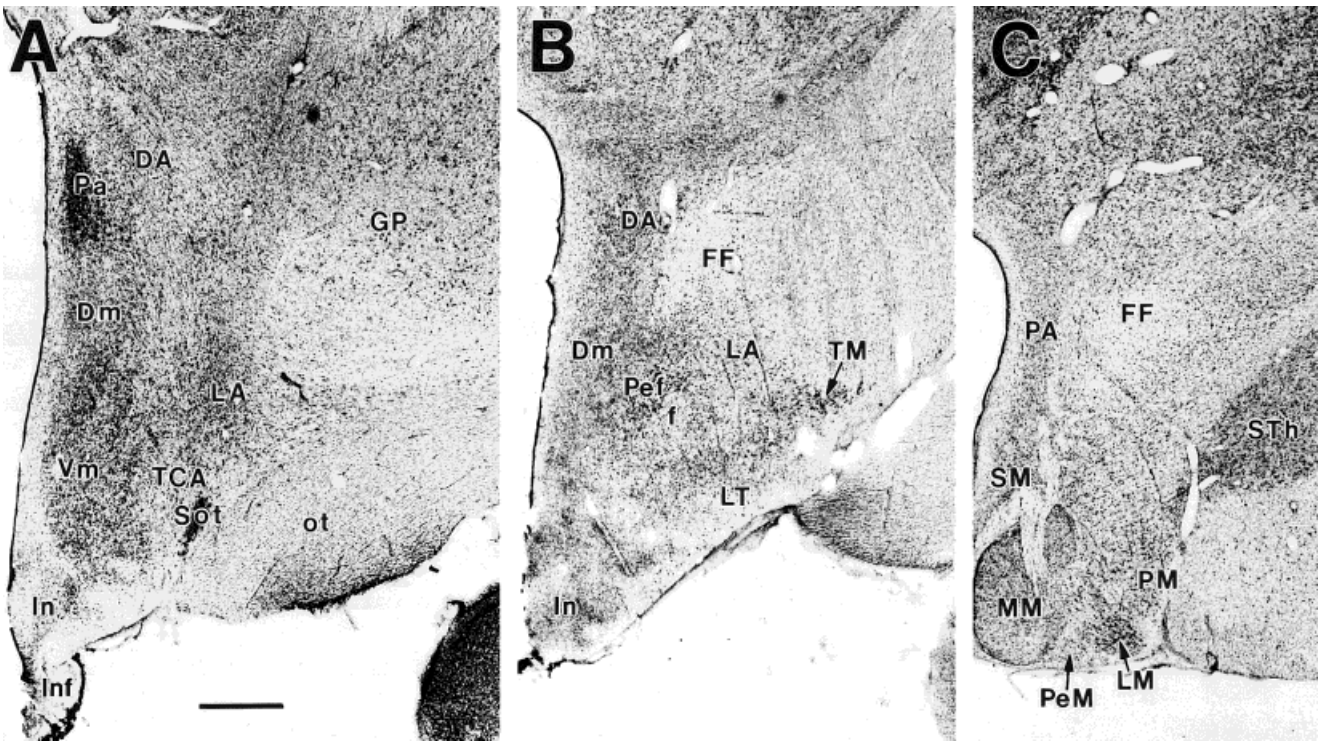


Fig. 2. Brightfield photomicrographs of coronal sections stained with cresyl violet taken from tuberal through posterior levels of the right side of the hypothalamus, showing the location of the various nuclei and areas and their cytoarchitecture. **A:** Section through the tuberal division of the hypothalamus showing the ventromedial nucleus (Vm). **B:** Section through the most caudal extent of the tuberal hypothalamus. **C:** Section through the posterior hypothalamus at the level of the medial mammillary nucleus (MM). For abbreviations, see list. Scale bar = 1 mm.

nucleus or area is based on where most of the neurons in that nucleus or area are located, but nuclei may extend to adjacent regions. For example, the posterior hypothalamic area (PA) is included in the medial division of the posterior hypothalamus, even though it often extends slightly into the tuberal hypothalamus.

Architecture of hypothalamic nuclei and areas

Photomicrographs of Nissl-stained sections of the monkey tuberal and posterior hypothalamus are shown in Figure 2. AChE-stained sections are shown in Figure 3. The following description focuses primarily on areas in the tuberal and posterior hypothalamus that had retrogradely labeled neurons or anterograde label after tracer injections in prefrontal areas. Little label was found in the anterior hypothalamus. The differential distribution of three neurochemical markers (Inhibitor-1, DARPP-32, and NADPH diaphorase) in the various hypothalamic nuclei and areas is described where these markers help distinguish adjacent areas. We describe these areas primarily following the nomenclature of Nauta and Haymaker (1969).

Tuberal hypothalamus

Lateral division. The LA extends from the anterior hypothalamus to midway through the medial mammillary nucleus (MM) and contains fibers of the medial forebrain bundle. The LA consists of a loosely packed, diverse group of cells, some of which are quite large, and some are AChE positive. (Figs. 2A,B, 3A,B, 14C).

Previous descriptions of other areas in the lateral division of the tuberal hypothalamus in the primate have varied considerably (Table 1). In particular, the term "tuberomammillary nucleus" (TM) has been used to refer to different areas. Malone (1914) first used the name in the human to describe large, diffusely scattered cells in the lateral hypothalamus, surrounding the fornix, and extending into the dorsal hypothalamus. Other architectonic studies in the human have described a similar distribution of tuberomammillary neurons (Le Gros Clark, 1936; Brockhaus, 1942; Nauta and Haymaker, 1969; Braak and Braak, 1992).

In the rat, the TM has been defined as the large cells clustered rostral and ventral to the lateral mammillary nucleus (LM; Saper, 1985). The rat TM also has been defined more broadly as the histaminergic neurons in the tuberal and posterior hypothalamus that also contain glutamic acid decarboxylase (GAD), galanin, and adenosine deaminase (Köhler et al., 1985; Staines et al., 1986; Ericson et al., 1987; for review, see Wada et al., 1991). Similar to the distribution of tuberomammillary neurons described by many investigators in the human, histaminergic cells in the rat are distributed in a ventrolateral cluster, a mediodorsal cluster, and a more diffuse collection extending between these two areas. The clusters of rat tubermammillary neurons have been divided into subgroups (Table 1, TM). In the human, the histamine-containing neurons of the tuberomammillary complex also are distributed in several clusters (Airaksinen et al.,

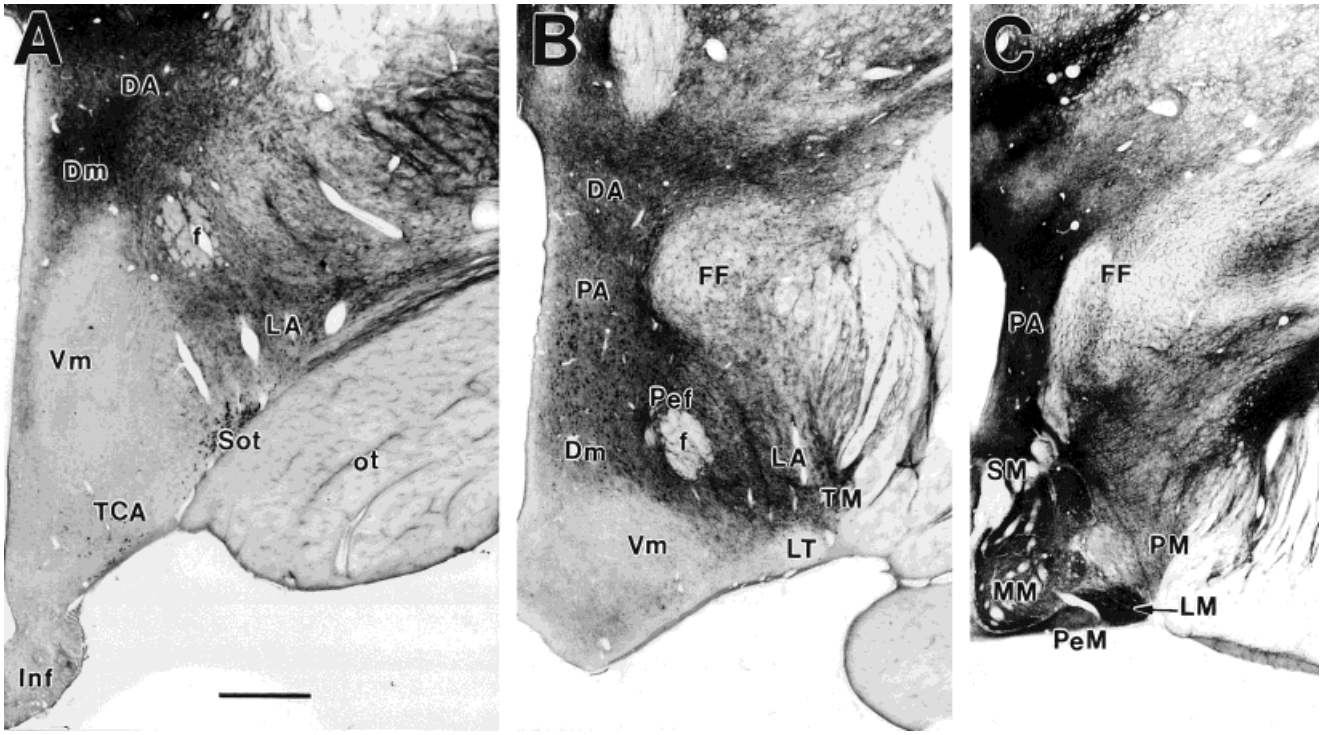


Fig. 3. Brightfield photomicrographs of coronal sections processed for acetylcholinesterase (AChE) taken from tuberal through posterior levels of the right side of the hypothalamus, showing the location of the various nuclei and areas. **A:** Section through the tuberal hypothalamus at the level of the ventromedial nucleus (Vm). **B:** Section through the caudal extent of the tuberal hypothalamus. **C:** Section through the posterior hypothalamus at the level of the medial mammillary nucleus (MM). For abbreviations, see list. Scale bar = 1 mm.

1991). Similarly, histamine-containing neurons in the monkey are found in the ventrolateral part of the tuberal and posterior hypothalamus, the LA, the PA, the DA, and the perifornical area as well as dorsal, medial, and lateral to the MM (Manning et al., 1996). We use the term "tuberomammillary complex" to refer to all the groups of histaminergic neurons. We reserve "TM" for the dense cluster of large neurons in the ventrolateral portion of the tuberomammillary complex in the tuberal division and rostral part of the posterior division of the hypothalamus, similar to the description of Saper (1990) of the TM in the human hypothalamus. The TM has large darkly staining cells in Nissl-prepared sections (Fig. 2B) that are positive for AChE (Fig. 3B). In our material, the neurons of the TM are positive for diaphorase and DARPP-32.

The lateral tuberal nucleus (LT) refers to a group of small pale cells along the ventral border of the tuberal hypothalamus (Fig. 2B), according to the nomenclature of several investigators (Malone, 1914; Papez and Aronson, 1934; Nauta and Haymaker, 1969; Saper, 1990; Braak and Braak, 1992). Other terms used for this area are listed in Table 1. Neurons of the lateral tuberal nucleus are not positive for AChE, but the nucleus contains a fine network of AChE-positive fibers (Fig. 3B). Many neurons of the lateral tuberal nucleus are positive for Inhibitor-1, and some are positive for DARPP-32.

Medial division. The area of the tuber cinereum (TCA) includes the loosely scattered, small to medium-sized cells beginning at the ventral border of the paraventricular nucleus and extending ventrally through the area lateral to the ventromedial nucleus and medial to the LA (Fig. 2A). It can be distinguished from the adjacent LA in myelin-stained sections, in which the LA is considerably darker. The TCA appears to correspond to the retrochiasmatic area in the rat (Swanson and Kuypers, 1980). The ventromedial nucleus (Vm) is clearly delineated in Nissl-stained material, surrounded by a relatively cell-free, narrow region (Fig. 2A). Dorsal to the ventromedial nucleus is the dorsomedial nucleus (Dm), which is a loose collection of neurons that is less differentiated in primates than in the rodent (Fig. 2A; Nauta and Haymaker, 1969). The fibers of the dorsomedial nucleus are positive for AChE, which clearly distinguishes this nucleus from the ventromedial nucleus (Fig. 3A). The DA is a loose collection of small, medium, and large cells situated at the dorsal extent of the anterior, tuberal, and posterior hypothalamus (Fig. 2A,B; Nauta and Haymaker, 1969). At the ventral border of the tuberal hypothalamus is the infundibular nucleus (Fig. 2A,B), also called the arcuate nucleus, which has fibers that are positive for DARPP-32 and neurons that are positive for Inhibitor-1 . The infundibular nucleus is situated dorsal to the infundibulum (Fig. 2A).

Posterior hypothalamus

Lateral division. Posteriorly, the LA looks much the same as it does anteriorly except that more neurons are AChE positive and the fibers stain darker in the posterior LA (Fig. 3B). The LA ends approximately midway through the rostrocaudal extent of the MM. In the monkey, the paramammillary nucleus (PM) lies medial to the cerebral peduncle, lateral to the LM, and caudal to the TM and was first described by Veazey et al. (1982). Architectonically, the PM has many features in common with the TM. Like

the TM, the PM has large, dark-staining cells in Nissl-prepared sections that are slightly smaller than the cells of the adjacent LM (Fig. 2C). Many neurons and fibers in the PM are AChE positive (Fig. 3C), and neurons in the PM appear to contain histamine (Manning et al., 1996) and thus are included along with the TM in the tuberomammillary complex. However, in the macaque monkey, the PM can be distinguished from the TM by several criteria. PM neurons are distinguished from the TM by their immunoreactivity for the AMPA receptor subunit, GluR1, unlike the more anterior TM neurons, which do not show GluR1 immunoreactivity (Ginsberg et al., 1995; Table 1). Furthermore, in our own studies, the PM contains some Inhibitor-1–positive neurons, unlike the TM. The PM and TM also can be distinguished on connectional grounds. The PM nucleus was first described as a separate nucleus by Veazey et al. (1982), partly on the basis of its fairly specific input from the central nucleus of the amygdala (Price and Amaral, 1981).

Medial division. The PA lies dorsomedially in the posterior hypothalamus (Fig. 2C) and consists of a somewhat triangular arrangement of small to large cells that are more closely grouped than cells in the adjacent LA (Nauta and Haymaker, 1969). The PA stains fairly dark for AChE, with an AChE-positive fiber plexus and some AChE-positive neurons, especially posteriorly (Fig. 3C). The perifornical nucleus (Pef) surrounds the fornix as it travels through the hypothalamus (Fig. 2B; Christ, 1969). Its medium to large cells stain darkly in Nissl-prepared sections, and both cells and fibers are positive for AChE (Fig. 3B). We also observed that the Pef stains darker for myelin than the PA.

The MM is surrounded by a fiber capsule, making it the most easily identifiable structure in the posterior hypothalamus (Fig. 2C). The supramammillary nucleus (SM) lies directly over the MM and is ventral to the PA (Nauta and Haymaker, 1969). The SM consists of cells that stain darkly for Nissl and are closely packed (Fig. 2C). It is largest at the caudal end of the MM and extends beyond it for a short distance. The fiber plexus of the SM stains darkly for AChE (Fig. 3C). The SM is positive for diaphorase, distinguishing it from the adjacent PA and the MM. Lateral and ventral to the MM is the LM. The LM consists of large cells that stain darkly for Nissl (Fig. 2C), and has a dense fiber plexus that stains darkly in myelin and AChE preparations (Fig. 3C; Veazey et al., 1982).

The perimammillary nucleus (PeM) lies between the MM and LM (Fig. 2C). In the rat, neurons ventral to the MM and LM are included in the tuberomammillary complex based on their neurochemical characteristics (Köhler et al., 1985; Ericson et al., 1987; Staines et al., 1987; Inagaki et al., 1990). However, in the human and the monkey, the PeM appears to be distinct from the TM. Nauta and Haymaker (1969) identified the PeM as a separate neural group from the TM and included it in their LM (Table 1) (see their Fig. 4–9). In our material, PeM is distinguishable from the more anterior and lateral TM. In Nissl-stained material, the PeM includes smaller, lighter staining neurons than the TM (Fig. 2C). In addition, the PeM contains very few AChE-positive neurons, whereas many neurons in the TM are AChE positive (Fig. 3C). The connections of the PeM also distinguish it from the TM. In the rat, the prefrontal cortices send projections only to the more lateral histaminergic TM neurons and not to the histaminergic neurons ventral to the MM that correspond to PeM (Wouterlood et al., 1987). As described below, in the present study we also found that prefrontal cortices issue projections to the TM but not the PeM.

Injection sites

Figure 4 is a composite diagram showing the location of injection sites of neural tracers in prefrontal cortices. The HRP injection sites were located in three medial areas (Fig. 4A: area 25, case AH; area 32, case AE; medial 9, case AO), seven lateral prefrontal areas (Fig. 4B: dorsal 10, case SF; ventral 46, cases MAV, MBH, and AA; dorsal 46, case AB; area 8, cases AC and AD), and five orbital areas (Fig. 4C: PAll/Pro, case AG; orbital Pro, case AF; area 11, cases MBJ and AM; orbital 12, case MBY). Two cases with HRP injections in lateral premotor cortices adjacent to prefrontal areas also were included in the study (dorsal area 6, cases MAO and MAL). Fluorescent dye injection sites were in medial areas 32 (case AKy), 32/24 (case AIb), medial 14 (cases AKb and DLb), and orbital area Pir/OLF T (case AIy). ^{3}H-labeled amino acid injections were placed in medial area 32 (case MDQ), lateral ventral area 46 (case MFF), and orbital area Pro (case MAR) and area 11 (case MFT). Cases with injections in medial and dorsolateral areas make up the mediodorsal group of cases. Cases with injections in orbital and ventrolateral areas are referred to as basoventral cases.

Most of the cases described here appeared in previous studies investigating connections with the amygdala (Barbas and De Olmos, 1990), thalamus (Barbas et al., 1991; Dermon and Barbas, 1994), hippocampal formation (Barbas and Blatt, 1995), or other cortical areas (Barbas, 1993; Barbas, 1995a). Recent studies use the identification codes we use here (Barbas, 1993; Dermon and Barbas, 1994; Barbas, 1995a; Barbas and Blatt, 1995; Barbas and Rempel-Clower, 1997) and refer to the designations used in older studies.

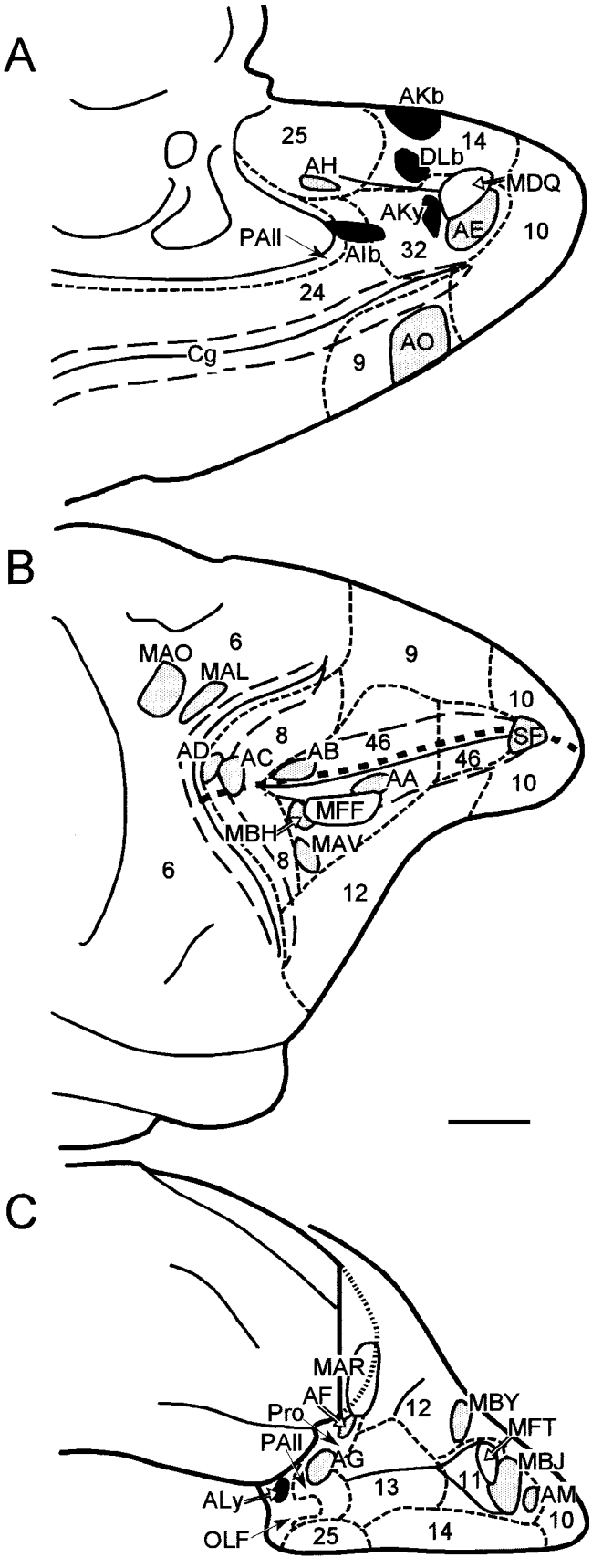
Origin of hypothalamic projections to prefrontal cortices

The distribution of labeled neurons in the ipsilateral hypothalamus after HRP injections in prefrontal areas is shown in Table 2 and in diagrams of cross sections in Figures 5–13. Labeled neurons were noted primarily in the posterior hypothalamus in all cases studied. Within the posterior hypothalamus, labeled neurons in all cases were found medially in the PA and Pef. Laterally in the posterior hypothalamus, neurons were consistently labeled in the LA, TM, and PM. Fewer labeled neurons were observed in the anterior and tuberal divisions of the hypothalamus in areas including the LA, DA, anterior hypothalamic area (AA), and the TCA. The distribution of labeled neurons within the hypothalamus in the various cases studied is described below. Quantitative analyses described here included only the HRP cases unless otherwise noted.

Medial hypothalamus

Posterior hypothalamic area and perifornical nucleus. The majority of labeled neurons within the medial division of the hypothalamus were located in its posterior region in all cases, in the PA and the Pef (Table 2). No differences in distribution were observed in these areas for the various cases.

Supramammillary nucleus and perimammillary nucleus. Most cases with injections in basoventral prefrontal areas (i.e., orbital and ventrolateral areas) had labeled neurons in the SM and the PeM (PeM; Table 2). Fewer labeled



neurons were observed in the SM and PeM after injections in mediodorsal areas (i.e., medial and dorsolateral areas).

Dorsal hypothalamic area. Most cases with prefrontal injections had labeled neurons in the DA (Table 2). As described above, the DA extends through much of the rostrocaudal extent of the hypothalamus. We found a different distribution of labeled neurons in the anterior, tuberal, and posterior divisions of the DA depending on the location of the injection site in prefrontal cortical areas. Injections in caudal orbital areas PAll/Pro and Pro (cases AG and AF) and medial areas 25 and 32 (cases AH and AE) resulted in a majority of labeled neurons in the tuberal division of the DA, followed by the anterior and posterior divisions (Figs. 5C,D; 8A–C; 9B–D). In contrast, all cases with injections in lateral prefrontal areas V46 and D8 had labeled neurons predominantly in the posterior division of the DA (cases MBH, AA, AB, AC; Figs. 12B and 13C). An intermediate pattern of distribution of labeled neurons in the DA was found after injections in orbital areas 11 and O12, and lateral area D10 (cases MBJ, AM, MBY, SF). In these cases a few labeled neurons were evident in the tuberal division, but most were found in the posterior division of the DA (Figs. 6B,C; 7A,C; 11B,C).

Anterior hypothalamic area and the area of the tuber cinereum. Very few neurons were labeled in the AA and the TCA after injections in prefrontal areas and premotor area 6 (Table 2).

Lateral hypothalamus

Lateral hypothalamic area. The LA contained at least 15% of the total ipsilateral hypothalamic projection neurons in all cases except 2 (cases AA and AC, with injections in areas V46 and D8, respectively; Table 2). Figure 14 shows retrogradely labeled neurons in the LA in cases AO (Fig. 14A) and AE (Fig. 14B). In most cases, labeled neurons were distributed throughout the anterior, tuberal, and posterior divisions of the LA. The rostrocaudal topography of projection neurons in the LA varied for injections in different prefrontal cortical areas. After injections in caudal orbital areas PAll/Pro and Pro, most labeled LA neurons were found in the anterior and tuberal divisions, followed by the posterior division (cases AG and AF; Fig. 5A,D,E). After injections in medial areas 25, 32, and M9 (cases AH, AE, AO) and area D10 (case SF), most labeled neurons were seen in the tuberal division, followed by the posterior and anterior divisions (Figs. 8–11). A third pattern of distribution, consisting of a majority of labeled neurons in the posterior division of the LA, occurred after injections in other prefrontal areas. Specifically, after injections in orbital areas 11 and O12, most labeled

Fig. 4. Composite of injection sites shown on the medial (**A**),lateral (**B**), and orbital (**C**) surfaces of the cerebral hemisphere. The injection sites are superimposed on an architectonic map of the prefrontal cortex (Barbas and Pandya, 1989). Shaded sites were injected with horseradish peroxidase conjugated to wheat germ agglutinin (HRP-WGA), black sites were injected with fluorescent dyes, and the outlined white sites were injected with ^{3}H-labeled amino acids. Mediodorsal areas include all medial areas (A) and the area above the heavy dashed line on the lateral surface (B). Basoventral areas include all areas on the orbital surface (C) and the area below the heavy dashed line on the lateral surface (B). The temporal pole is removed from the orbital view (C) to show an injection site in caudal orbital area proisocortex (Pro). Fine dashed lines demarcate architectonic areas indicated by numbers. PAll, Pro, and OLF also indicate architectonic areas. Other letter combinations refer to cases (see Results, Injection sites for details). Scale bar = 5 mm.

TABLE 2. Distribution of Labeled Neurons in the Ipsilateral Hypothalamus after Injection of HRP-WGA[1]

		Hypothalamic projection zone										
		Medial							Lateral			
Case	Injection site	AA	TCA	PA	Pef	SM	PeM	DA	LA	TM	PM	Total *N*
Basoventral												
AG	PAll/Pro	—	2	8	2	2	4	3	15	10	54	62
AF	Pro	2	2	21	6	8	4	4	15	16	22	48
MBJ	11	—	—	25	12	2	—	3	19	19	20	251
AM	11	—	—	18	15	3	—	7	22	13	22	68
MBY	O12	—	<1	35	12	3	5	5	21	8	10	194
MAV	V46	—	2	26	3	—	17	—	27	6	19	86
MBH	V46	—	1	27	23	1	1	4	27	5	11	106
AA	V46	—	—	24	13	3	11	3	3	16	27	37
Mediodorsal												
AH	25	—	—	24	11	2	3	27	23	10	—	62
AE	32	1	2	27	20	1	1	5	20	18	5	543
AO	M9	3	—	13	4	—	—	—	39	18	23	94
SF	D10	—	—	20	26	1	—	3	32	12	6	181
AB	D46	—	—	25	17	—	—	8	17	25	8	12
AC	D8	—	—	38	24	—	1	2	9	22	4	92
AD	D8	—	—	25	11	—	—	—	32	10	22	84
Premotor												
MAL	6	—	—	24	8	—	—	—	15	20	33	51
MAO	6	—	—	—	—	—	—	—	62	19	19	27

[1]Data in columns below area or nucleus designations are expressed in percentages. The last column (total *N*) shows the total number of labeled neurons in the hypothalamus in each case; —, areas with no evidence of labeled neurons. For abbreviations, see list.

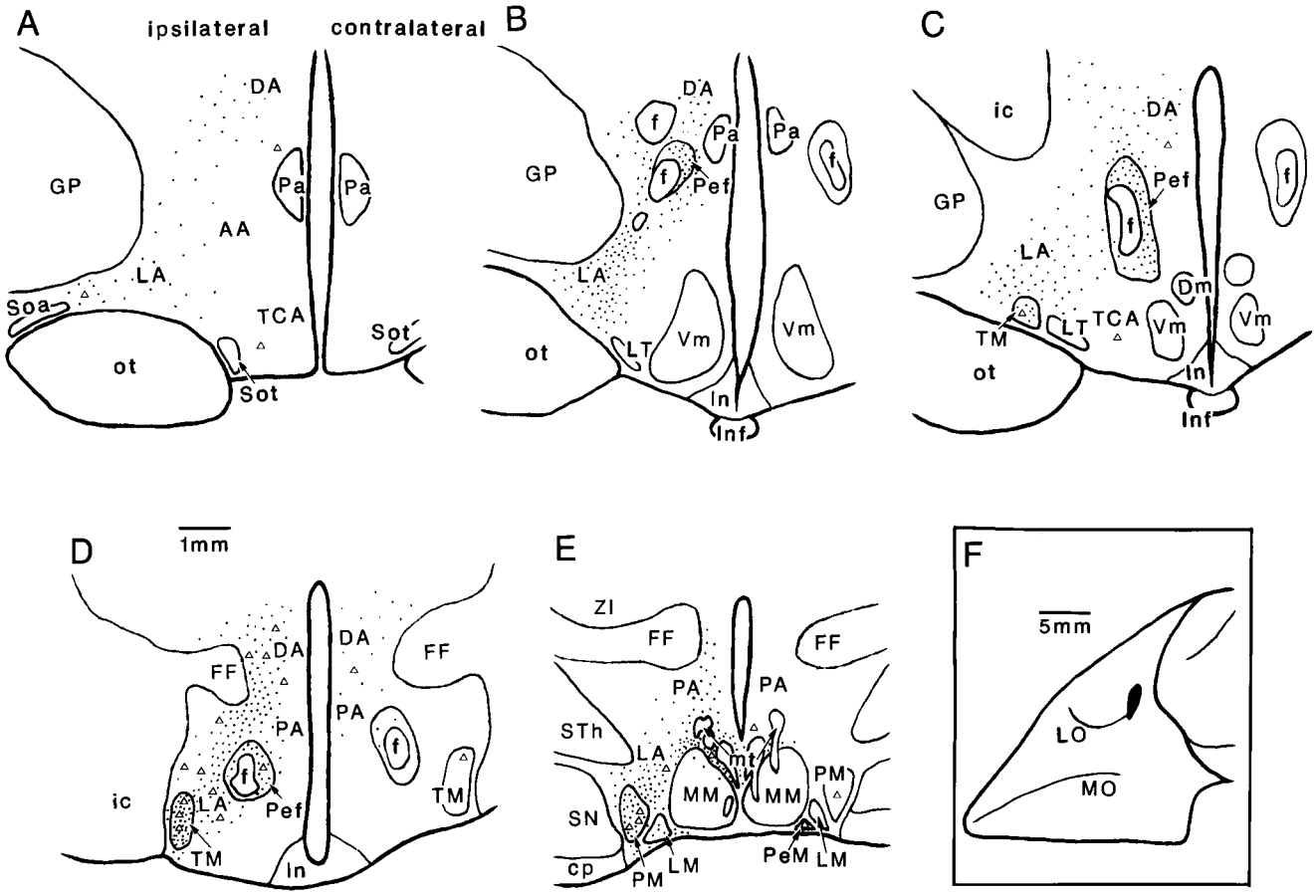


Fig. 5. The distribution of labeled neurons (△) and anterograde label (•) in diagrams of coronal sections in anterior through posterior (**A–E**) hypothalamic levels in case AF after horseradish peroxidase (HRP) injection in orbital area Pro (black area in **F** shows the injection site). In this figure and all remaining figures, each triangle represents 1–2 retrogradely labeled neurons; the number of dots represents the relative density of anterograde label n. For abbreviations, see list.

neurons were found in the posterior division of the LA, followed by the tuberal and anterior divisions (cases MBJ, AM, MBY; Figs. 6 and 7). This pattern was more pronounced for cases with injections in lateral prefrontal areas V46 and D8. Cases MAV, MBH, AC, and AD had very few or no evidence of labeled neurons in the anterior LA,

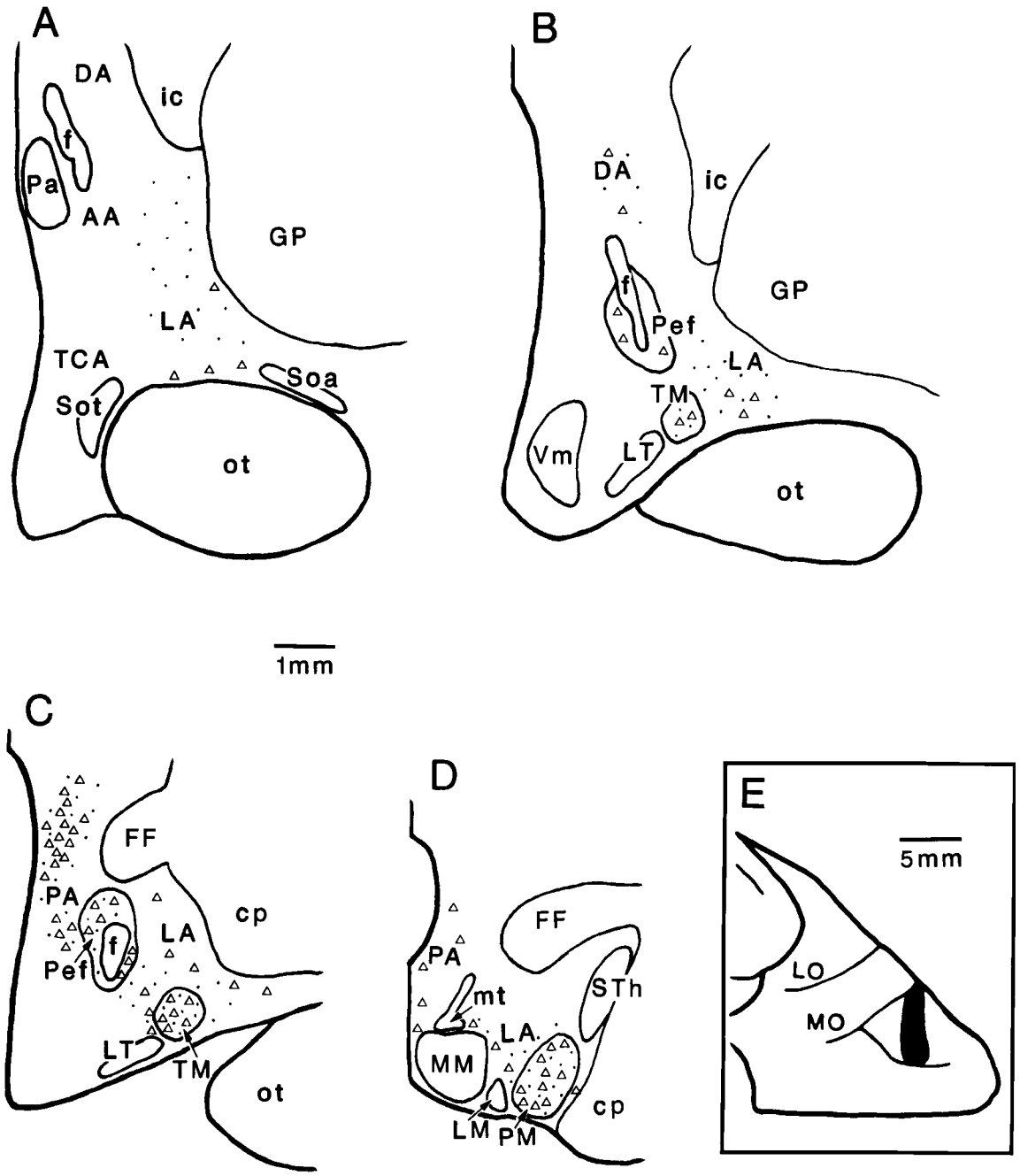


Fig. 6. The distribution of labeled neurons and anterograde label in the anterior through posterior hypothalamus (**A–D**) in case MBJ after a horseradish peroxidase (HRP) injection in orbital area 11 (**E**). For abbreviations, see list.

and cases AA and AC had only one or two labeled neurons in the entire LA (Fig. 13B,C).

Tuberomammillary nucleus and paramammillary nucleus. Almost all cases had labeled neurons in the TM and the PM (Figs. 5C–E, 6B–D, 7C,D, 8B,C, 9C–E, 10C,D, 11B–D, 12B,C, 13B–G). The one exception was case AH (medial area 25), which had no labeled neurons in the PM (Table 2). Differences in distribution were noted for the basoventral cases compared with the mediodorsal. All basoventral cases had more projection neurons in the PM than the TM (Table 2). In contrast, most mediodorsal cases had more labeled neurons in the TM than PM except cases AO and AD (medial area 9 and area 8; Table 2).

Contralateral projections from the hypothalamus

Five cases had the contralateral side available for analysis (cases AG, area PAll/Pro; AF, area Pro; AM, area 11; AE, area 32; AO, area M9; in other cases, the contralateral side was used for other experiments), and all five had retrogradely labeled neurons in the contralateral hypo-

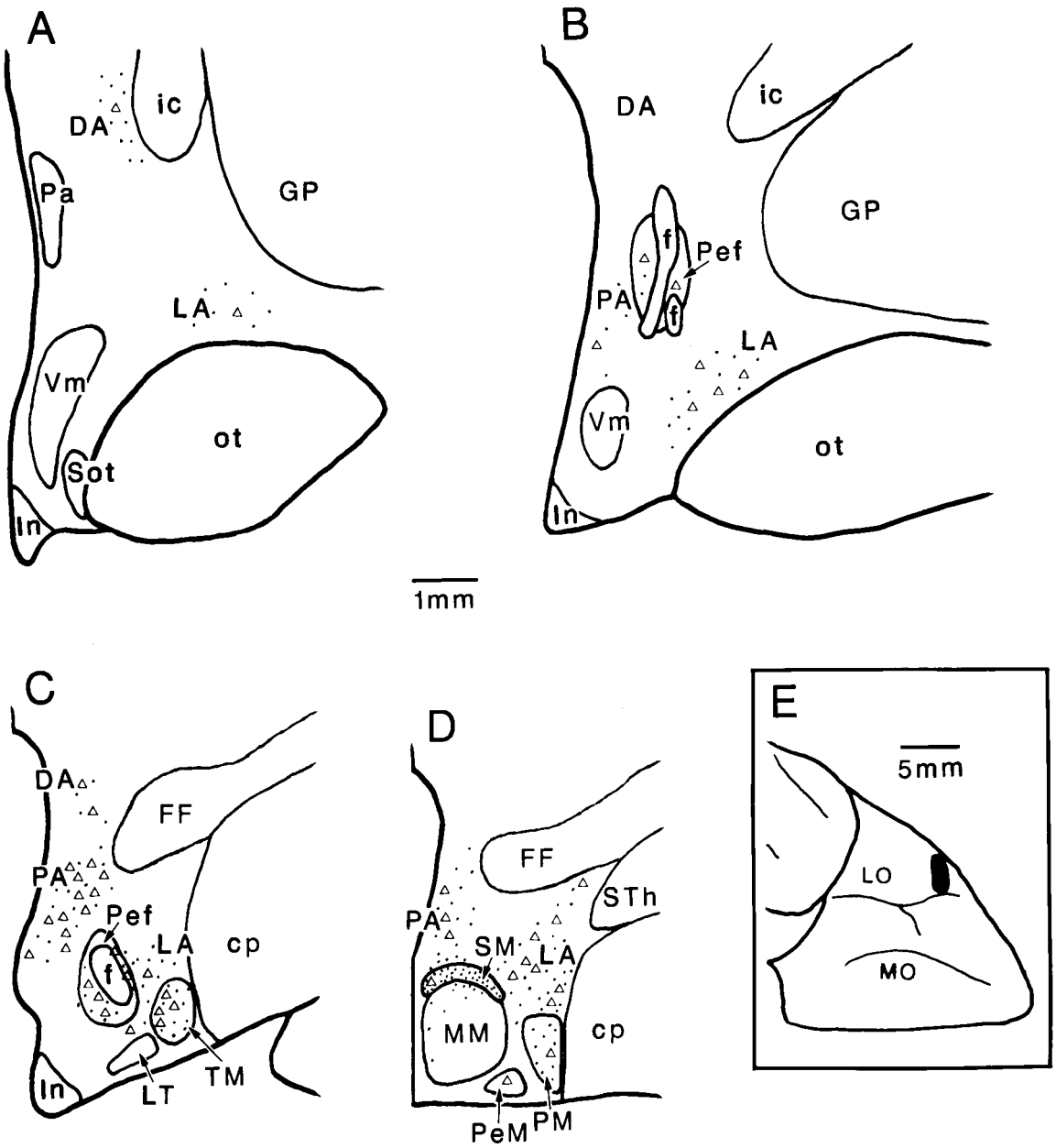


Fig. 7. The distribution of labeled neurons and anterograde label in the tuberal through posterior hypothalamus (**A–D**) in case MBY after a horseradish peroxidase (HRP) injection in orbital area 12 (**E**). For abbreviations, see list.

thalamus (Table 3; Figs. 5, 9, and 10). A sixth case (AH, injection in area 25) had the contralateral side available, but it was excluded from the analysis because the halo of the injection spread somewhat into the contralateral hemisphere and we could not rule out the possibility that some HRP was transported from the contralateral area 25.

Most hypothalamic nuclei and areas that had ipsilateral retrogradely labeled neurons also contained labeled neurons contralaterally. The number of labeled neurons in the contralateral hypothalamus is shown in Table 3, where it is also expressed as a percentage of the number of labeled neurons in the ipsilateral side (numbers in parentheses). In the medial portion of the hypothalamus, contralateral labeled neurons were found in the PA, Pef, AA, SM, PeM, and DA. In the medial hypothalamus, all five cases had retrogradely labeled neurons in the contralateral PA (mean of five cases; the number of contralateral labeled neurons was 41% of labeled neurons in the ipsilateral PA). The two cases with medial injection sites (cases AE and AO)—but not the cases with orbital injection sites—had labeled neurons in the contralateral Pef and the AA. Two of the three cases with labeled neurons in the ipsilateral PeM also had labeled neurons on the contralateral side (cases AF and AE). Only case AM (area 11) had labeled neurons in the contralateral SM. Finally, cases AE and AG had label in the contralateral DA.

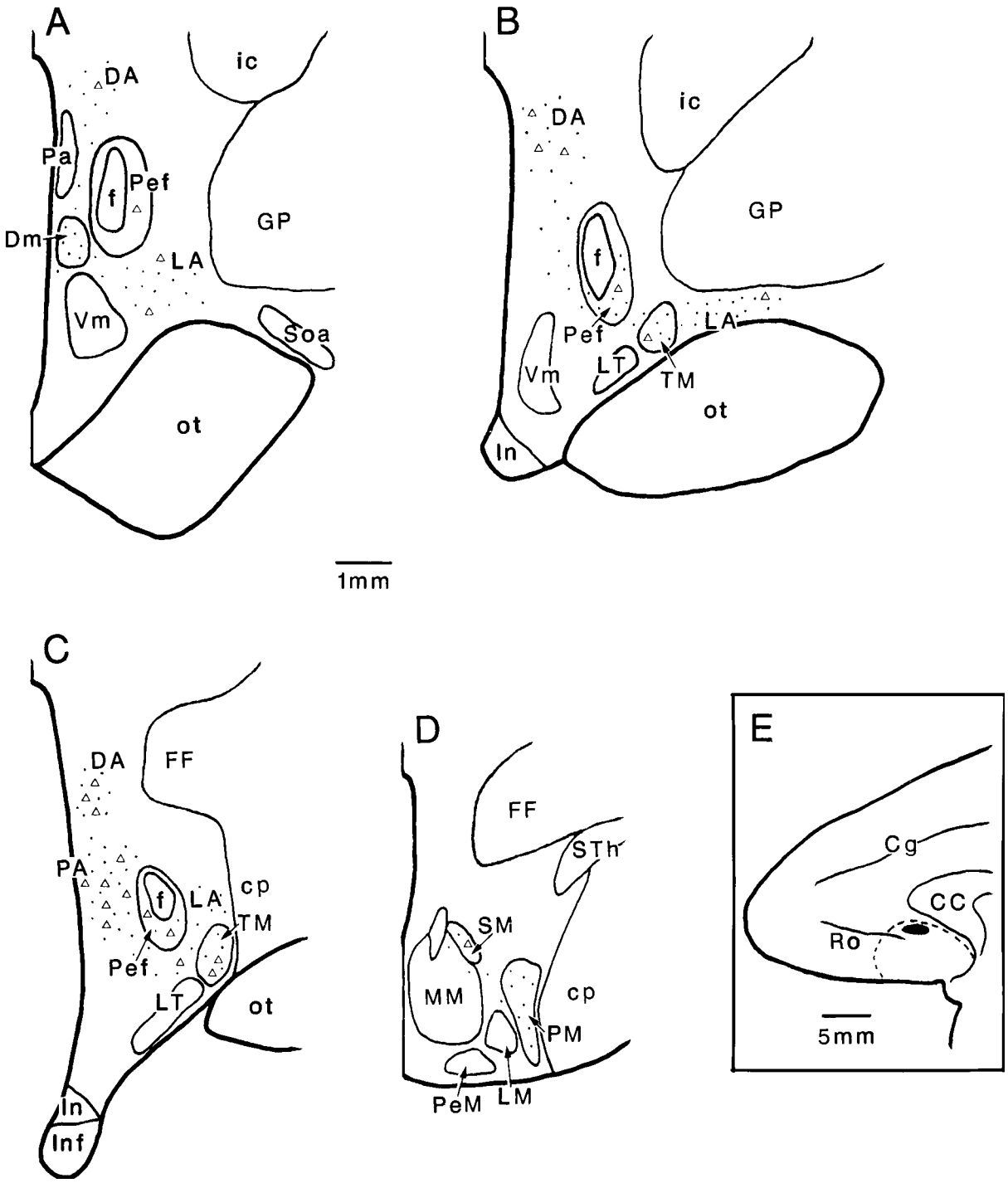


Fig. 8. The distribution of labeled neurons and anterograde label in the tuberal through posterior hypothalamus (**A–D**) in case AH after a horseradish peroxidase (HRP) injection in medial area 25 (**E**). For abbreviations, see list.

In the lateral part of the hypothalamus, contralateral labeled neurons were observed in the LA, TM, and PM. Three of the five cases had retrogradely labeled neurons in the tuberal and posterior divisions of the contralateral LA, but not in the anterior LA. Four cases had labeled neurons in the contralateral TM. All five cases had labeled neurons in the contralateral PM (mean contralateral label in PM = 16% of ipsilateral PM).

Termination of prefrontal projections in the hypothalamus

Anterograde label was evident in the ipsilateral hypothalamus after injection of HRP or ^{3}H-labeled amino acids in several prefrontal areas (Table 4). Some anterograde label was also apparent in the contralateral hypothalamus in cases that had ipsilateral anterograde label. Three cases

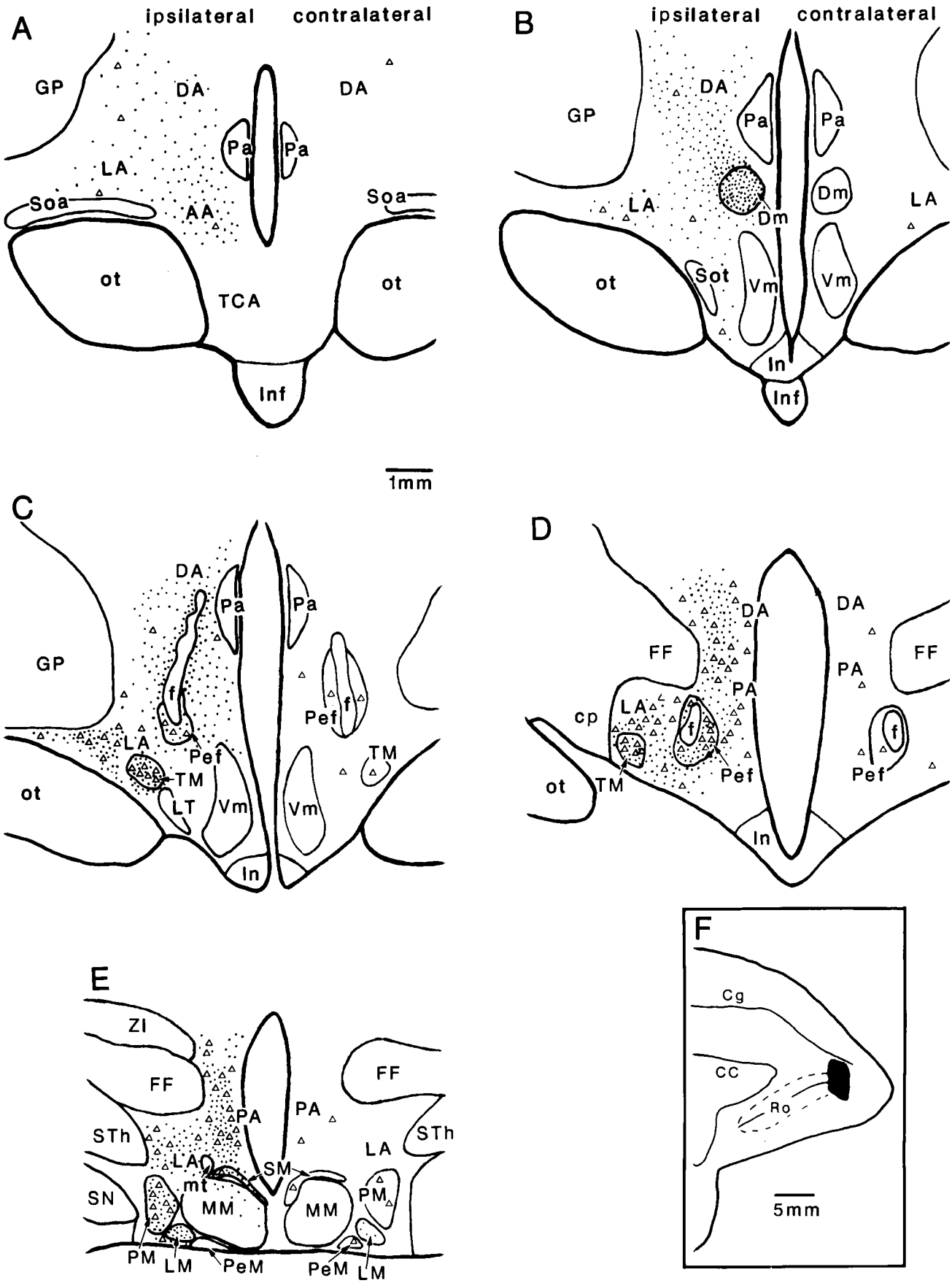


Fig. 9. The distribution of labeled neurons and anterograde label in the anterior through posterior hypothalamus (**A–E**) in case AE after a horseradish peroxidase (HRP) injection in medial area 32 (**F**). For abbreviations, see list.

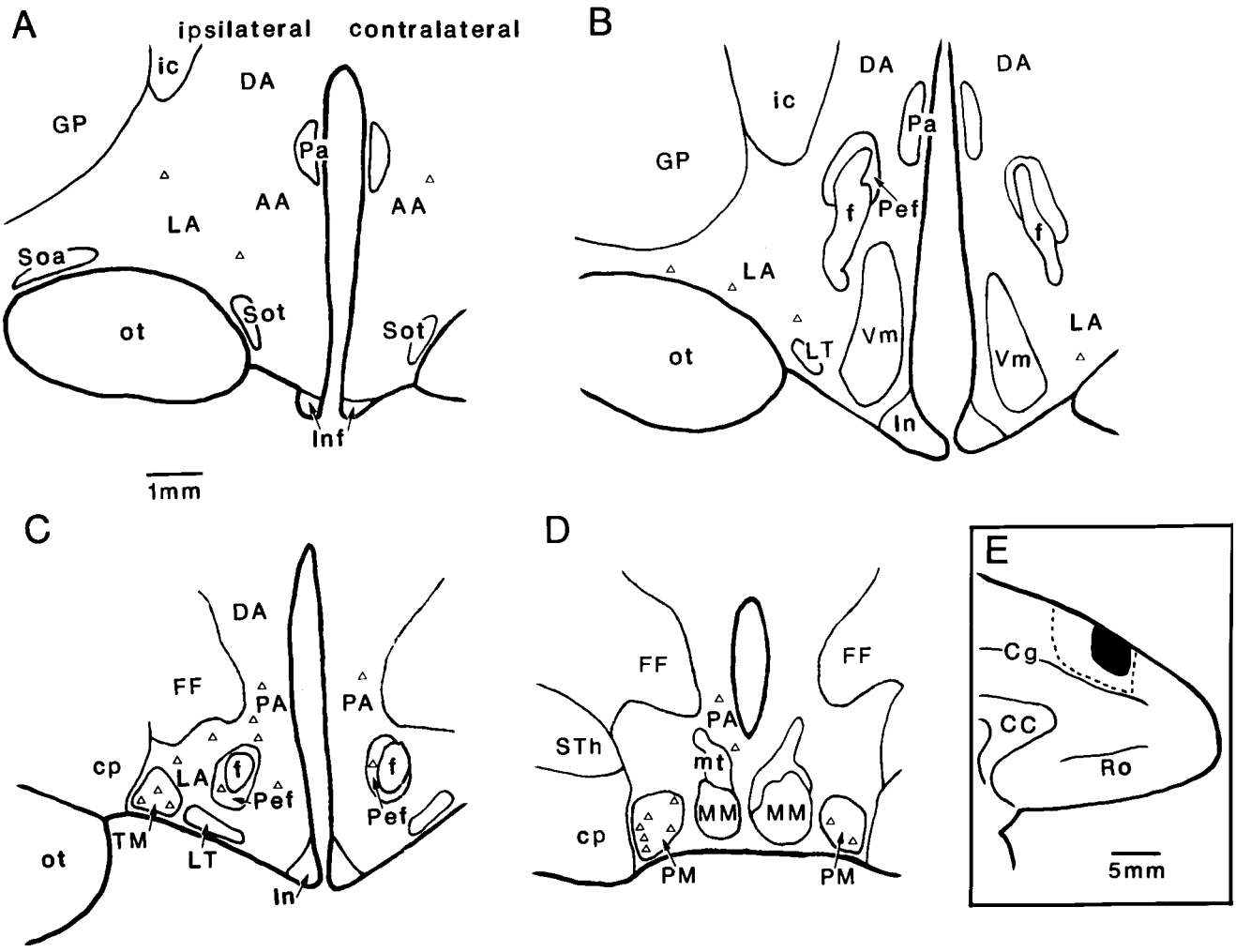


Fig. 10. The distribution of labeled neurons in the anterior through posterior hypothalamus (**A–D**) in case AO after a horseradish peroxidase (HRP) injection in medial area 9 (**E**). For abbreviations, see list.

with the most ipsilateral anterograde label throughout the hypothalamus had injections in orbital area Pro and medial area 32 (cases AF, MAR, and AE; Figs. 5, 9, 14B, and 15). Injections in orbital areas 11 and O12 also resulted in substantial anterograde label (cases MBJ, AM, MFT, MBY; Figs. 6 and 7). However, injections in mediodorsal areas in M9 and D10 (cases AO and SF) appeared to result in much less or no anterograde label in the hypothalamus (Figs. 10, 11, 14A). Similarly, in seven cases with injections in lateral prefrontal areas (areas 46 and 8), there was little evidence of anterograde label in the hypothalamus (Figs. 12 and 13B–D). In four of these cases, there was no evidence of anterograde label (cases AA, MFF, AB, AD; Table 4). Likewise, cases with injections in premotor area 6 (MAL, MAO) appeared to have little or no anterograde label in the hypothalamus (Fig. 13E–G).

Anterograde label was detected in the LA in all cases that had anterograde label apparent anywhere in the hypothalamus. Figure 14 shows anterograde label in the LA in case AE (Fig. 14B) and an absence of anterograde label in case AO (Fig. 14A). In the nine cases with moderate to heavy anterograde label in the hypothalamus overall (area Pro, cases AF and MAR; area 11, cases MBJ, AM, and MFT; area O12, case MBY; area 25, case AH; area 32, cases AE and MDQ), label was distributed in the LA, PA, Pef, DA, SM, TM, and PM (Figs. 5–9, 15). Interestingly, only cases with injections in medial areas 25 and 32 had anterograde label in the dorsomedial nucleus (cases AH, AE, and MDQ; Figs. 8A and 9B). Other areas with occasional label included the AA, MM, and LM. Most of the areas in which anterograde label was observed also contained retrogradely labeled neurons. However, in the MM, LM, and dorsomedial nucleus, there was no evidence of labeled neurons, even though these areas occasionally contained anterograde label (e.g., Figs. 5E; 7D; 9B,E; 13D,G). The SM had relatively more dense anterograde than retrograde label in several cases (e.g., Figs. 7D and 11D).

Relationship of injection size to retrograde and anterograde label

We investigated whether the number of retrogradely labeled neurons or the density of anterograde label was related to the size of the tracer injection for cases injected

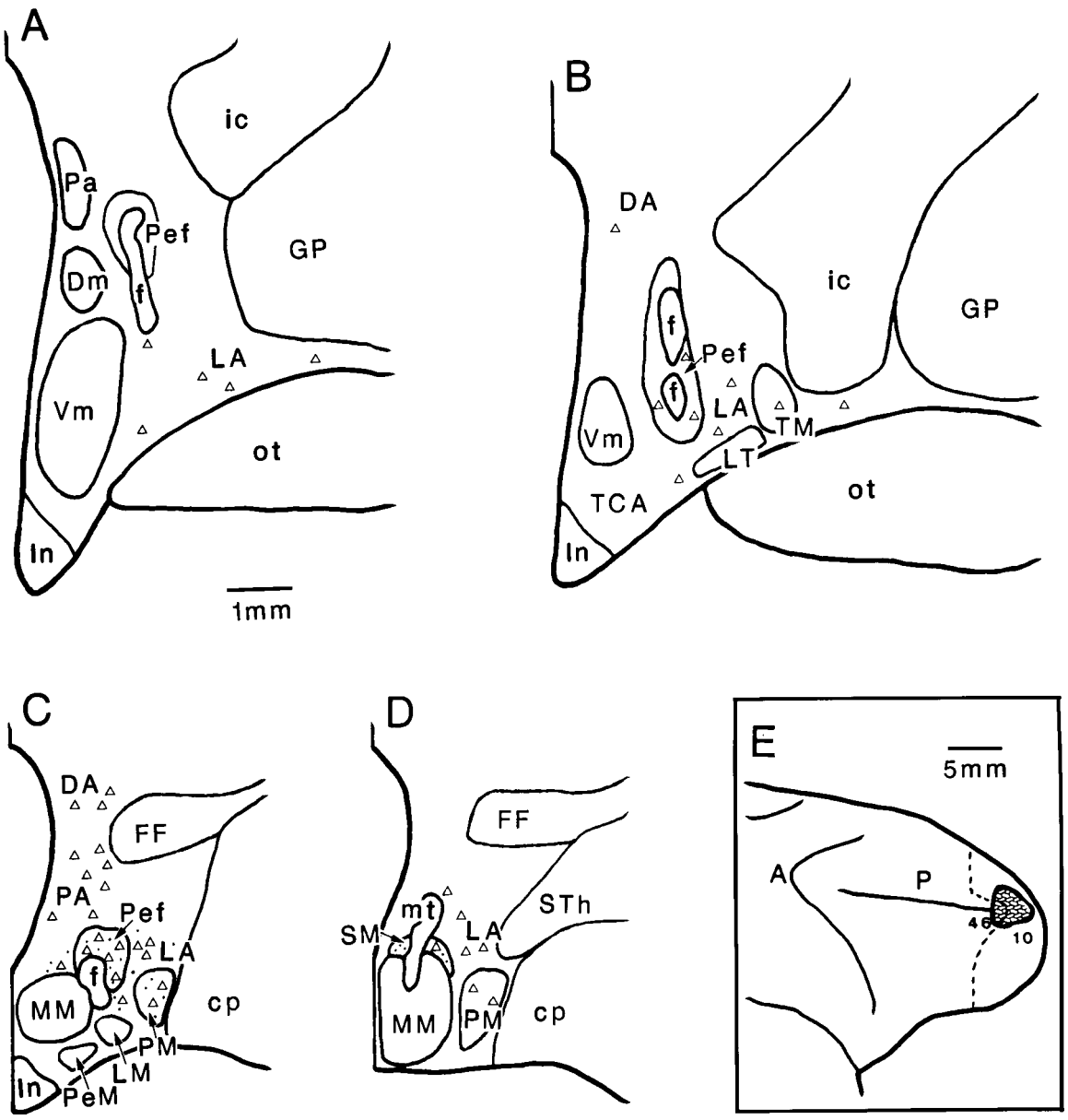


Fig. 11. The distribution of labeled neurons and anterograde label in the tuberal through posterior hypothalamus (**A–D**) in case SF after a horseradish peroxidase (HRP) injection in dorsal area 10 (also extending slightly into rostral area 46; **E**). For abbreviations, see list.

with HRP. There was a significant correlation between the size of the injection and the number of retrogradely labeled neurons in the hypothalamus (Spearman rank order correlation [r] = 0.69; $P < 0.05$). This finding suggests that approximately the same number of neurons in the hypothalamus overall project to each area of prefrontal cortex. In contrast, injection size was not positively correlated with the density of anterograde label in the hypothalamus (Spearman r = –0.03; $P > 0.05$), indicating that projections from the prefrontal cortices to the hypothalamus are highly specific, unlike the reciprocal projections. The differences in the density of anterograde label among cases were not related to the size of the injection, but to the location of injection.

Topographic differences related to the laminar definition of prefrontal cortices

General topography. We investigated whether there were differences in the hypothalamic connections of cortices with distinct structure, in addition to differences among specific cortical regions. The following overall analysis involved all cases with retrogradely labeled neurons in four or more sections, including cases with fluorescent dye as well as with HRP (a total of 17 cases). General differences in the rostrocaudal topography of labeled neurons were apparent after injections in prefrontal limbic cortices (levels 1–2) compared with eulaminate cortices (levels 3–5; Fig. 1 indicates cortical levels of prefrontal areas). Figure 16

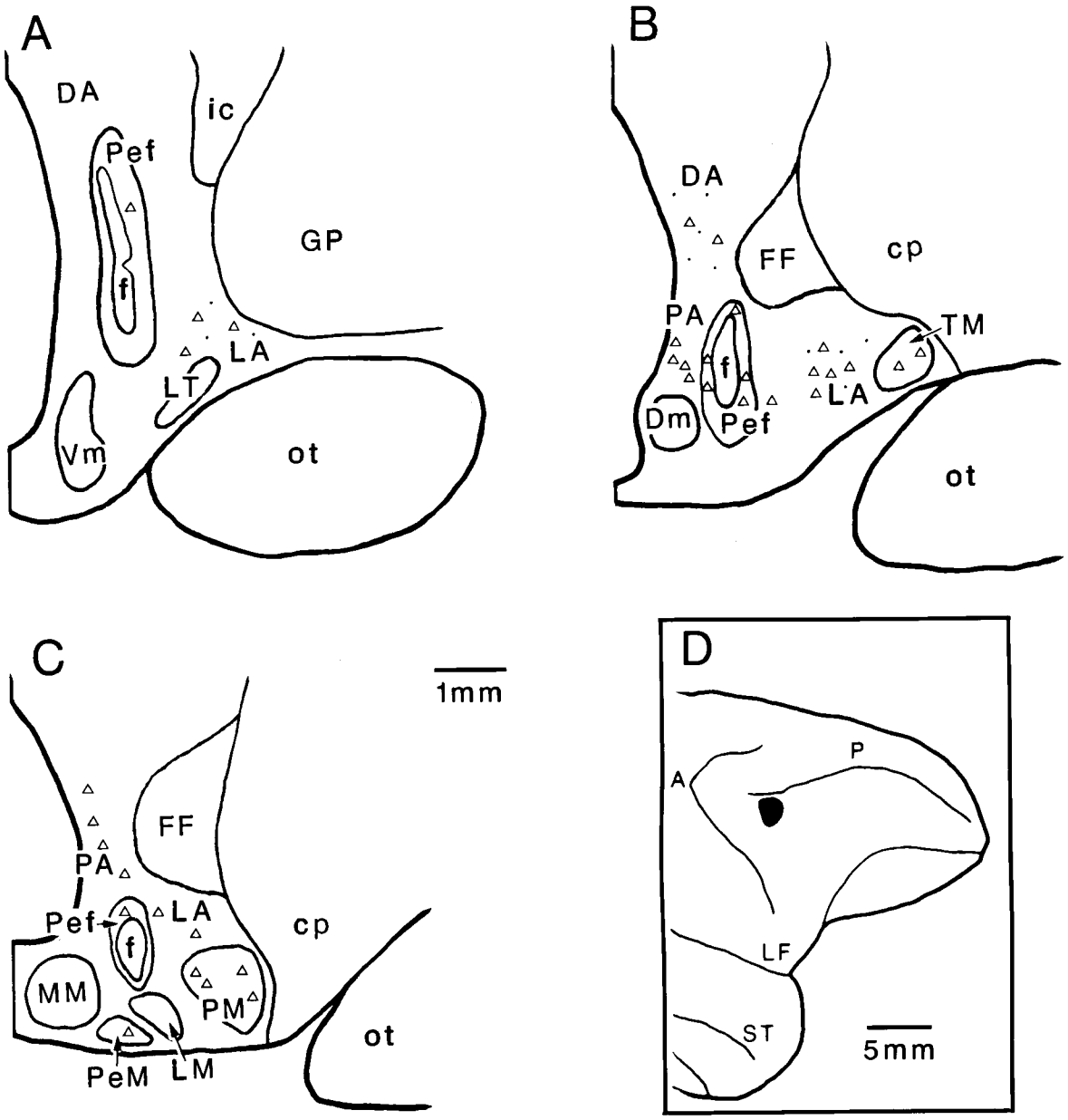


Fig. 12. The distribution of labeled neurons and anterograde label in the tuberal through posterior hypothalamus (**A–C**) in case MBH after a horseradish peroxidase (HRP) injection in lateral ventral area 46 (**D**). For abbreviations, see list.

shows the topography of projection neurons directed to prefrontal areas of different cortical levels. The majority of hypothalamic neurons projecting to all prefrontal areas originated in the posterior division of the hypothalamus. Cases with injections in lateral eulaminate areas (level 5 cortex; cases MAV, MBH, AA, AB, AC, AD) had very few labeled neurons in the anterior and tuberal hypothalamus. In contrast, cases with injections in limbic areas (levels 1–2; cases AG, AF, AIy, AH, AE, AIb) had higher proportions of labeled neurons in the anterior and tuberal hypothalamus. Prefrontal areas of cortical levels 3–4 (cases MBJ, AM, MBY, AKb, AO, SF) had an intermediate pattern of rostrocaudal label, with fewer projection neurons in the anterior and tuberal hypothalamus than limbic areas but more than level 5 eulaminate areas.

Thus, it appears that limbic prefrontal areas have more distributed input from the rostrocaudal axis of the hypothalamus, whereas the vast majority of hypothalamic projection neurons directed to level 5 eulaminate areas originated in the posterior hypothalamus. Injections in premotor area 6 showed a different rostrocaudal pattern of projection neurons from the lateral prefrontal areas (area 6, cases MAL and MAO, mean of 3% labeled neurons in anterior, 38% in tuberal, and 59% in posterior hypothalamus). The area 6 pattern more closely resembled that of prefrontal limbic areas.

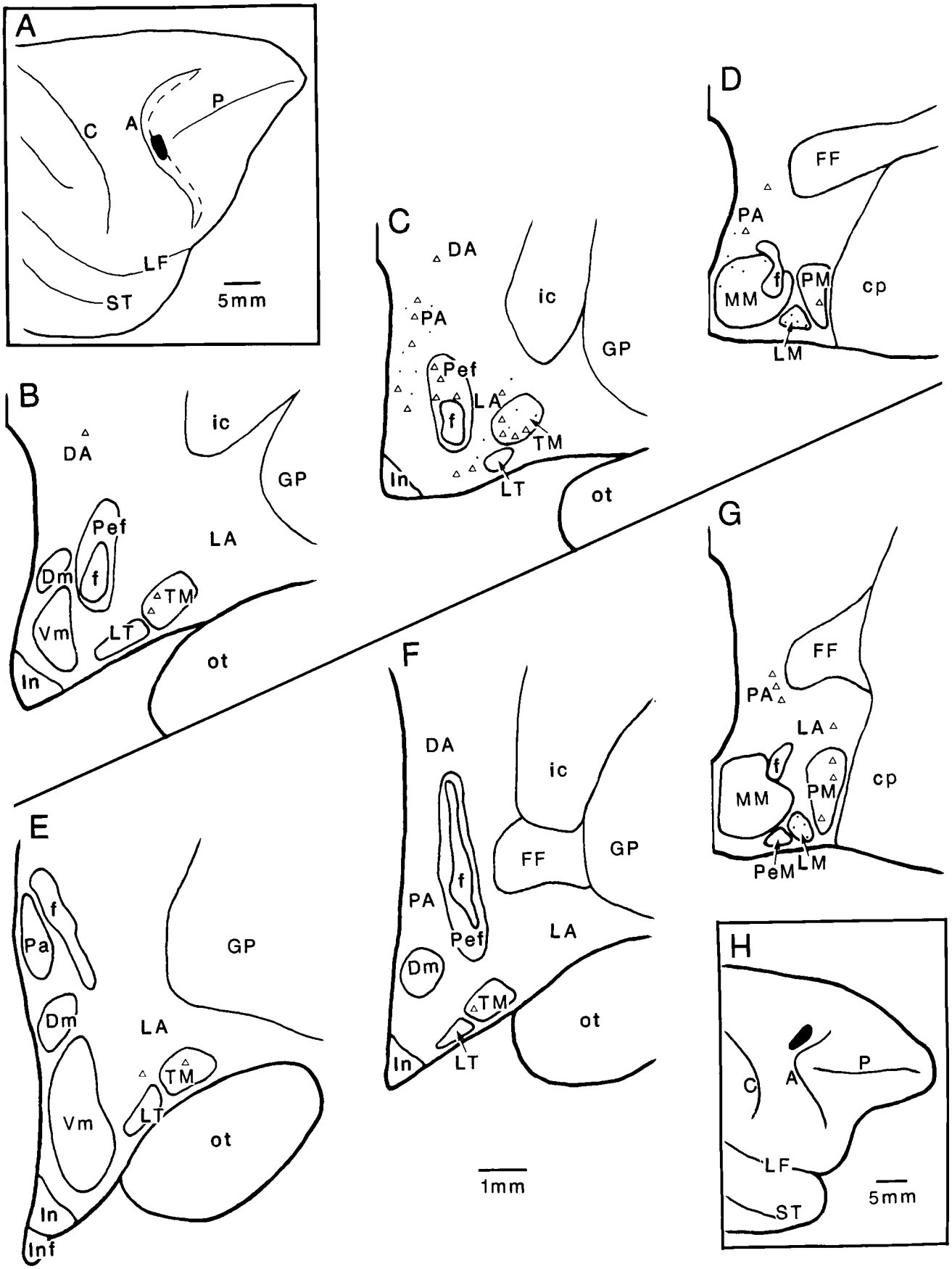


Fig. 13. The distribution of labeled neurons and anterograde label in the tuberal through posterior hypothalamus (**B–D**) in case AC after a horseradish peroxidase (HRP) injection in dorsal area 8 (**A**). The distribution of labeled neurons and anterograde label in the tuberal through posterior hypothalamus (**E–G**) in case MAL after an HRP injection in premotor area 6 (**H**). For abbreviations, see list.

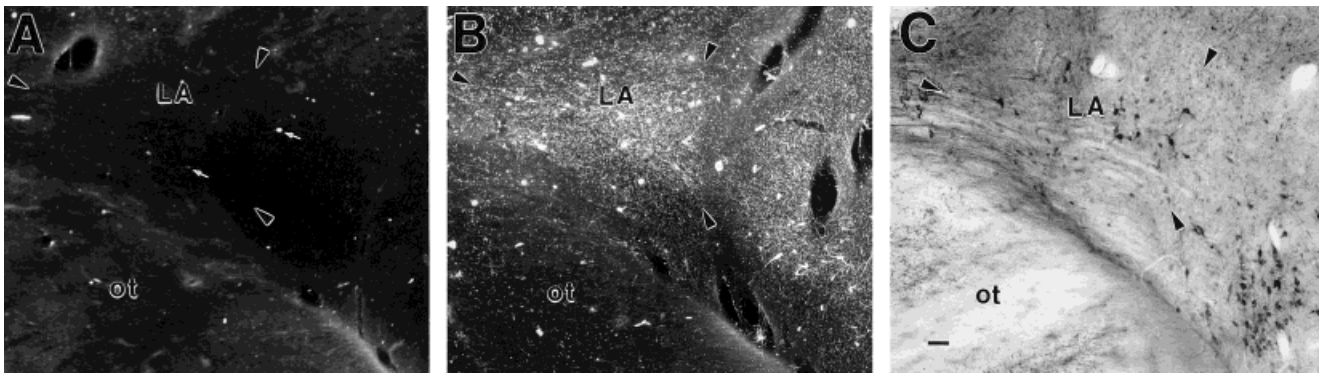


Fig. 14. Darkfield photomicrographs of the lateral hypothalamic area (LA) in two cases. **A:** Absence of anterograde label in the LA (arrowheads) after injection of horseradish peroxidase (HRP) in medial area 9 (case AO). Small arrows, retrogradely labeled neurons. **B:** Dense anterograde label (white dots) and retrogradely labeled neurons in the LA after injection of HRP in area 32 (case AE). **C:** Brightfield photomicrograph of AChE-positive neurons in a matched section through the LA in case AE. Scale bar = 100 μm (applies to all).

TABLE 3. Distribution of Labeled Neurons in the Contralateral Hypothalamus After Injection of HRP-WGA[1]

		Hypothalamic projection zone									
		Medial						Lateral			Total
Case	Injection site	AA	PA	Pef	SM	PeM	DA	LA	TM	PM	*N*
Basoventral											
AG	PAll/Pro	—	4 (80)	—	—	—	2 (100)	5 (56)	1 (20)	4 (12)	16 (26)
AF	Pro	—	7 (70)	—	—	1 (50)	—	—	1 (20)	3 (30)	12 (25)
AM	11	—	1 (8)	—	1 (50)	—	—	—	—	1 (7)	3 (4)
Mediodorsal											
AE	32	1 (25)	20 (14)	4 (4)	—	2 (67)	2 (7)	5 (5)	5 (5)	4 (15)	43 (8)
AO	M9	1 (50)	4 (33)	5 (125)	—	—	—	3 (8)	1 (6)	4 (18)	18 (19)

[1]Data in columns below area or nucleus designations are the numbers of retrogradely labeled neurons. The last column (total *N*) shows the total number of labeled neurons in the contralateral hypothalamus. The numbers in parentheses are the percentages of the number of ipsilateral labeled neurons; —, areas with no evidence of labeled neurons. For abbreviations, see list.

TABLE 4. Distribution of Anterograde Label in the Ipsilateral Hypothalamus

		Hypothalamic termination zone										
		Medial								Lateral		
Case	Injection site	AA	Dm	PA	Pef	SM	MM	LM	DA	LA	TM	PM
Basoventral												
AG	PAll/Pro	−	−	−	−	+	−	−	−	+	−	++
AF	Pro	−	−	++	++	+++	++	++	++	+++	++	+++
MAR[1]	Pro	−	−	+	++	++	−	+	++	+++	++	++
MBJ	11	+	−	+	+	+	−	−	++	++	+	++
AM	11	+	−	+	+	+	++	+	++	++	+	+
MFT[1]	11	+	−	+	+	+	−	−	++	++	+	+
MBY	O12	+	−	++	+	++	+	+	++	++	++	++
MAV	V46	−	−	+	−	+	−	+	+	+	+	+
MBH	V46	−	−	−	−	−	−	−	+	+	−	−
AA	V46	−	−	−	−	−	−	−	−	−	−	−
MFF[1]	V46	−	−	−	−	−	−	−	−	−	−	−
Mediodorsal												
AH	25	+	+	+	+	+	−	−	++	++	+	+
AE	32	++	++	+++	+++	++	++	++	+++	+++	+++	++
MDQ[1]	32	−	++	+	+	+	−	−	+	+	+	+
AO	M9	−	−	−	−	−	−	−	−	−	−	−
SF	D10	−	−	+	+	+	−	−	+	+	+	+
AB	D46	−	−	−	−	−	−	−	−	−	−	−
AC	D8	−	−	+	+	−	+	+	−	+	+	−
AD	D8	−	−	−	−	−	−	−	−	−	−	−
Premotor												
MAL	6	+	−	−	−	−	−	+	+	+	−	−
MAO	6	−	−	−	−	−	−	−	−	−	−	−

[1]Cases with injection of ^{3}H-labeled amino acids; all other cases had injections of WGA-HRP. +, light anterograde label; ++, moderate anterograde label; +++, dense anterograde label; −, no evidence of anterograde label. For abbreviations see list.

Additional differences were apparent in the general mediolateral topography of hypothalamic projection neurons to limbic prefrontal areas (Fig. 17). The following analysis also included both fluorescent dye and HRP cases, as described above. Cases with injection sites in orbital limbic areas (level ≤ 2, areas PAll, Pro, Pir/OLF T; cases AG, AF, AIy) had more labeled neurons in the lateral part of the hypothalamus than in the medial part ($P < 0.05$).

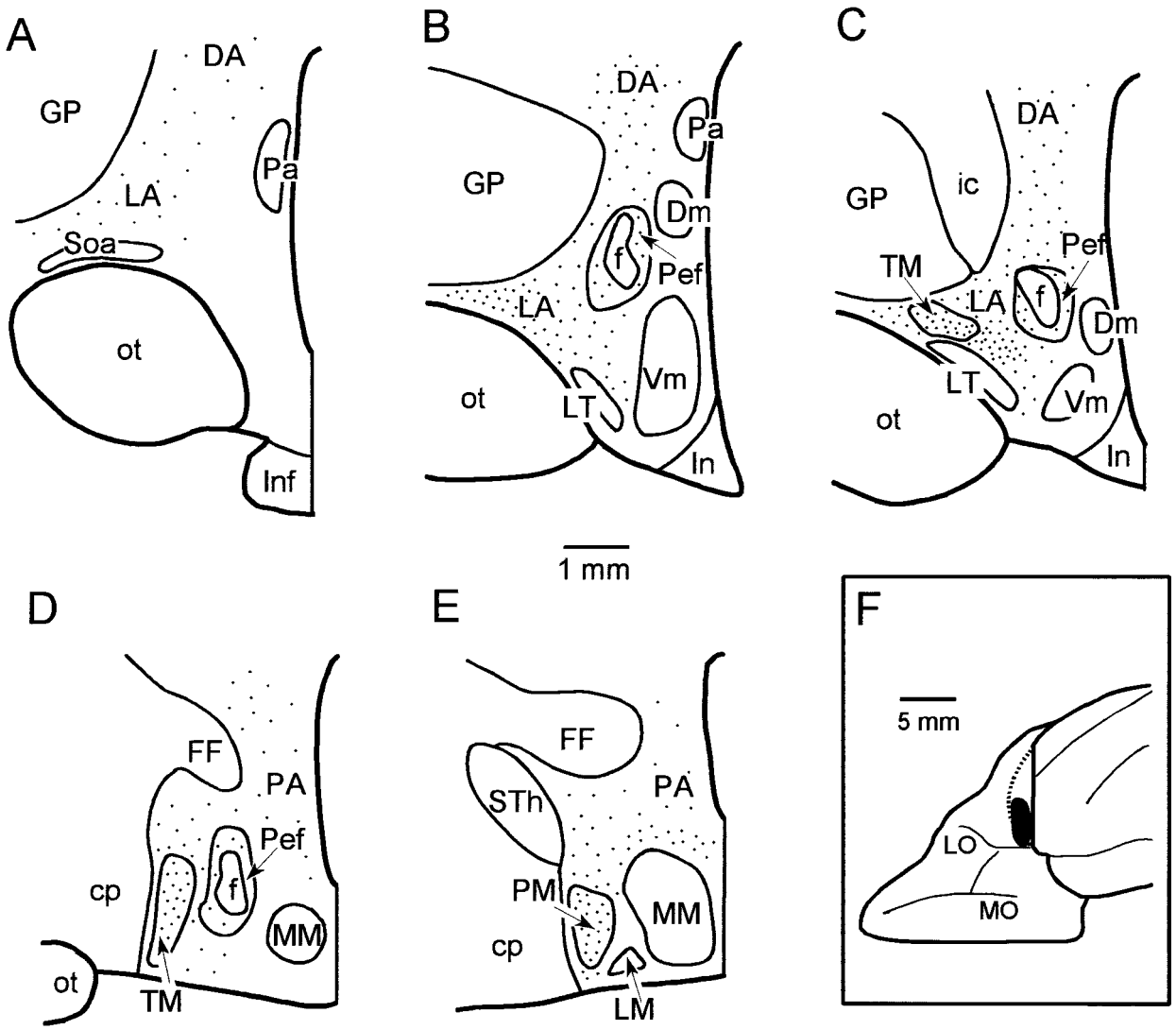


Fig. 15. The distribution of anterograde label (dots) in the anterior through posterior hypothalamus (**A–E**) in case MAR after an injection of ^{3}H-labeled amino acids in orbital area Pro (**F**). For abbreviations see list.

The opposite pattern occurred for hypothalamic projection neurons directed to medial limbic areas (level ≤ 2). Cases with injections in medial limbic areas (areas 25, 32, 32/24; cases AH, AE, AIb) had more labeled neurons in the medial than in the lateral hypothalamus ($P < 0.01$).

Mediolateral differences were not apparent for cases with injections in eulaminate prefrontal areas (Fig. 17). After injections in eulaminate areas (level ≥ 3), there were approximately equal numbers of projection neurons in lateral and medial regions of the hypothalamus, regardless of whether the injection was in basoventral areas (areas 11, O12, and V46; cases MBJ, AM, MBY, MAV, MBH, AA) or mediodorsal areas (areas 14, M9, D10, D46, and 8; cases AKb, AO, SF, AB, AC, AD). Cases with injections in premotor area 6 (cases MAL and MAO; not shown in Fig. 17) showed a different mediolateral distribution pattern of labeled neurons than cases with injections in the adjacent prefrontal area 8. Specifically, the area 6 cases had a majority of labeled neurons in the lateral part of the hypothalamus (Table 2).

Lateral and dorsal hypothalamic areas. The LA and DA extend across the anterior, tuberal, and posterior divisions of the hypothalamus. In our initial analysis, we found differences in the rostrocaudal topography of projection neurons in these areas directed to specific prefrontal sites. Here we investigated whether these differences were related to the level of laminar definition of the cortical area in which the injection was made.

We first compared the rostrocaudal topography of labeled neurons in the LA after injections in cortical areas of different levels of laminar definition. Because different patterns were apparent for injections in basoventral areas compared with mediodorsal areas, these groups of cases were treated separately. After injections in limbic orbital areas PAll/Pro and Pro (levels 1–2; cases AG, AF), most LA projection neurons were found in the anterior, followed by the tuberal and the posterior divisions of the hypothalamus (Fig. 18A). The opposite pattern of distribution occurred after injections in orbital areas 11 and O12, with a majority of labeled neurons in the posterior division

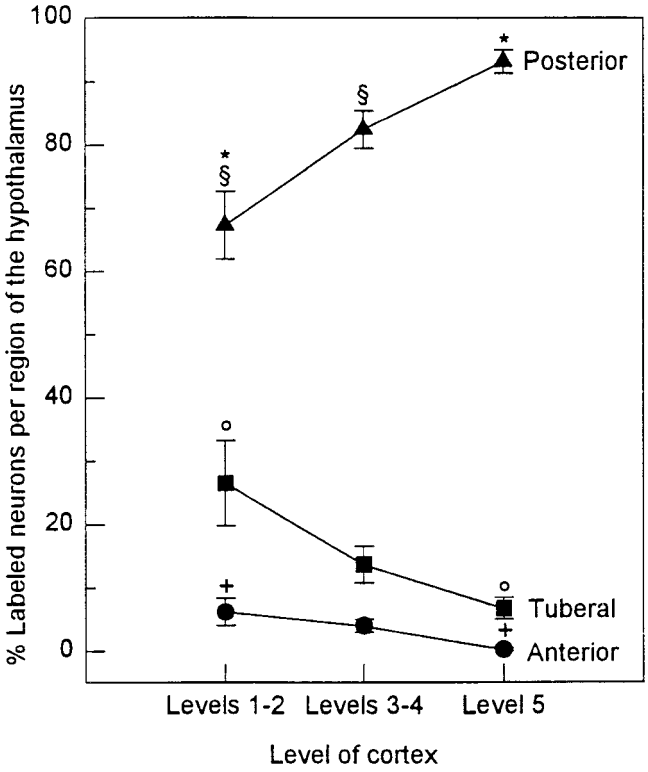


Fig. 16. Graph showing the percentage of labeled neurons distributed in the anterior (●), tuberal (■), and posterior (▲) divisions of the hypothalamus after tracer injections in limbic (levels 1–2, cases AG, AF, AIy, AH, AIb, and AE) and eulaminate areas (levels 3–4, cases MBJ, AM, MBY, AKb, AO, and SF; level 5, cases MAV, MBH, AA, AB, AC, and AD). Error bars are ± S.E.; matched symbols indicate significant differences between groups ($P < 0.05$).

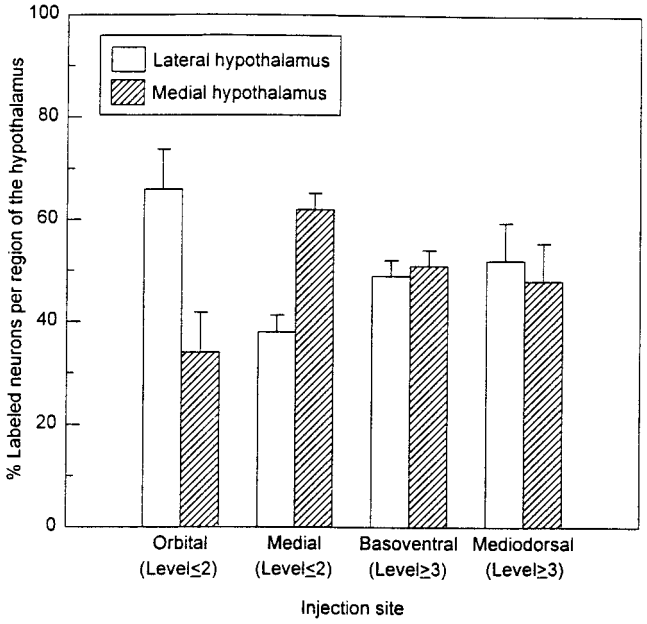


Fig. 17. Graph showing the percentage of labeled neurons in the lateral and medial divisions of the hypothalamus after retrograde tracer injections in orbital and medial limbic areas and basoventral and mediodorsal eulaminate areas. Injections in orbital limbic areas resulted in more retrogradely labeled neurons in the lateral hypothalamus ($P < 0.05$), whereas injections in medial limbic areas produced more labeled neurons in the medial hypothalamus ($P < 0.01$). Error bars are ± S.E.

(level 3; cases MBJ, AM, MBY). This pattern became more pronounced for level 5 basoventral areas (cases MAV, MBH; area V46; case AA had only one labeled neuron in the LA and thus was excluded from the analysis).

The distribution of LA neurons projecting to mediodorsal prefrontal areas followed a somewhat different pattern (Fig. 18B). Cases with medial injection sites (in areas of levels 1–2, areas 25 and 32 [cases AE, AH]; and levels 3–4, areas M9 and D10 [cases AO, SF]) had a majority of labeled neurons in the tuberal division, followed by the posterior and anterior divisions. The distribution of projection neurons directed to prefrontal eulaminate areas in level 5 was similar for basoventral and mediodorsal injection sites. After injections in mediodorsal level 5 areas, labeled neurons were noted primarily in the posterior division of the LA, but there was no evidence of labeled neurons in the anterior division (area D8; cases AC, AD; case AB had only two labeled neurons in the LA and was thus excluded from the analysis).

The distribution of labeled neurons in the anterior, tuberal, and posterior divisions of the DA also differed for injections in limbic and eulaminate prefrontal cortices (Fig. 19). The pattern of labeled neurons appeared to be the same for cases with similar laminar structure, irrespective of their location in basoventral or mediodorsal areas. Thus, in cases with injections in limbic areas (levels 1–2; areas PAll, Pro, 25, and 32; cases AG, AF, AH, AE) the majority of labeled neurons were noted in the tuberal division of the DA, followed by the anterior and posterior divisions. In contrast, cases with injections in level 5 eulaminate areas (areas 46 and 8; cases MBH, AA, AB, AC) had labeled neurons only in the posterior division of the DA. An intermediate pattern of labeled neurons in the DA was found with injections in level 3–4 areas (areas 11, O12, and D10; cases MBJ, AM, MBY, SF). In these cases, a few labeled neurons were observed in the tuberal division of the DA but most labeled neurons were found in the posterior division.

DISCUSSION

Ascending projections from hypothalamus differ according to prefrontal destination

The findings presented in this paper indicate that the hypothalamus has widespread projections to all sectors of the prefrontal cortex. Retrogradely labeled neurons in the hypothalamus were found for every tracer injection on the orbital, medial, and lateral surfaces. Most projection neurons originated in the posterior hypothalamus and it appeared that a significant proportion of the projections were contralateral as well as ipsilateral. These data confirm and extend previous findings in primates of the origin of hypothalamic projections to various cortices (Kievit and Kuypers, 1975; Jacobson et al., 1978; Potter and Nauta, 1979; Mizuno et al., 1982; Tigges et al., 1982; Mesulam et al., 1983; Tigges et al., 1983; Morecraft et al., 1992). In the first such study, Kievit and Kuypers (1975) noted that injections of HRP in parietal and lateral prefrontal areas labeled neurons in posterior levels of the

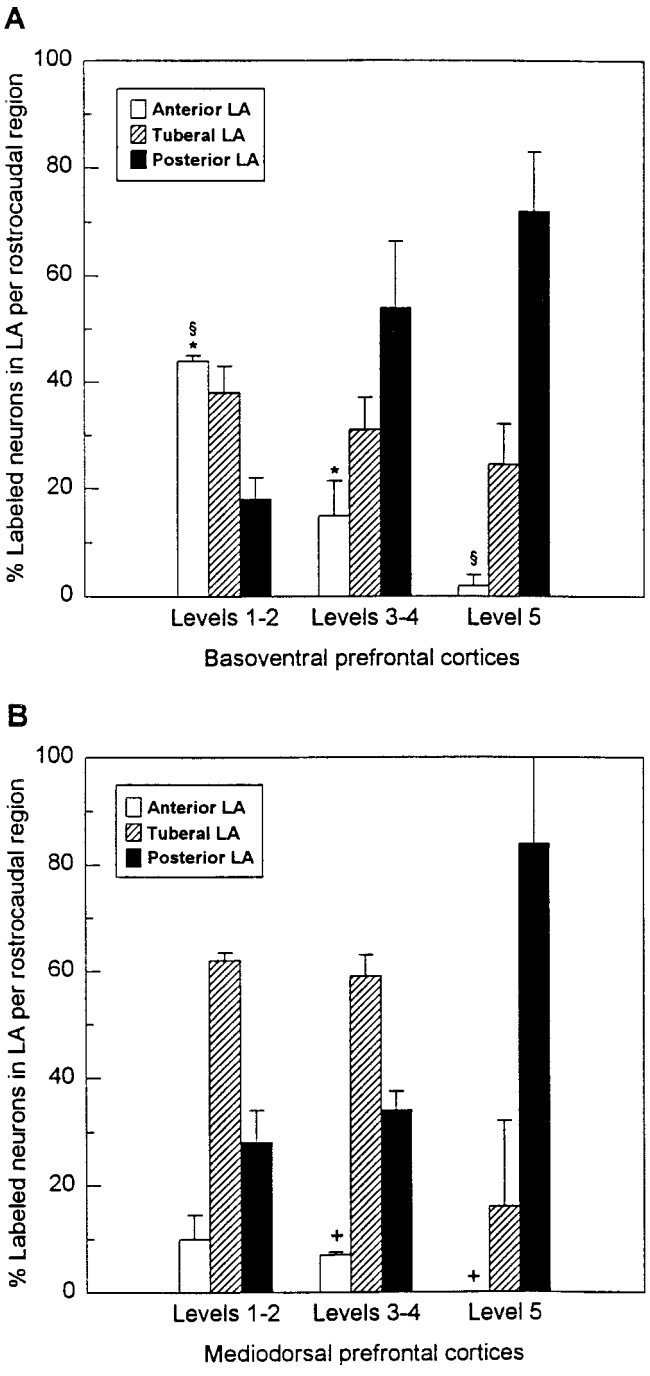


Fig. 18. Graphs showing the percentage of labeled neurons in the lateral hypothalamic area (LA) distributed in the anterior, tuberal, and posterior divisions after injections in prefrontal limbic areas (levels 1–2) and eulaminate areas (levels 3–4 and level 5). **A:** Basoventral cases; **B:** mediodorsal cases. Error bars are ± S.E.; matched symbols indicate significant differences between groups ($P < 0.05$).

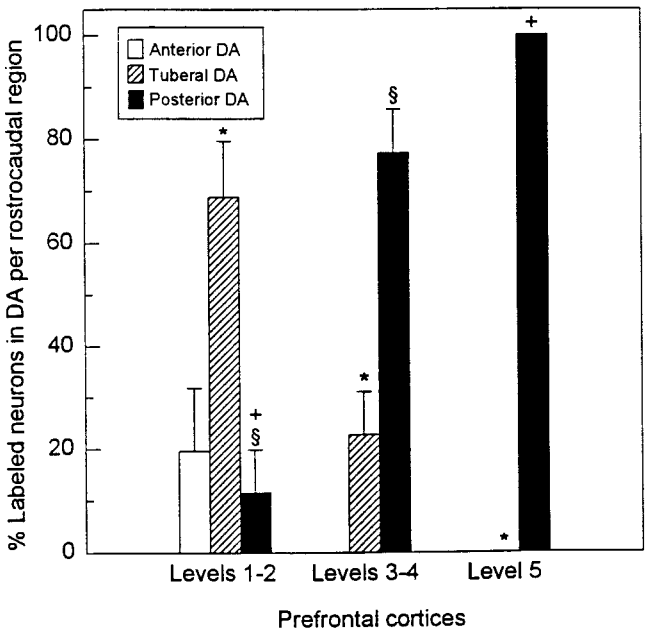


Fig. 19. Graph showing the percentage of labeled neurons in the dorsal hypothalamic area (DA) distributed in the anterior, tuberal, and posterior divisions after injections in prefrontal limbic areas (cortical levels 1–2) and eulaminate areas (levels 3–4 and level 5). Error bars are ± S.E.; matched symbols indicate significant differences between groups ($P < 0.05$).

hypothalamus in the lateral area, around the fornix, and dorsally in the medial hypothalamus. Subsequent studies indicated that a wide variety of cortical sites received projections from dorsomedial and lateral areas of the posterior hypothalamus, some of which originated from the contralateral side (Mizuno et al., 1982; Tigges et al., 1982; Mesulam et al., 1983; Tigges et al., 1983). Studies with injections in orbital and lateral prefrontal areas reported essentially the same findings (Jacobson et al., 1978; Potter and Nauta, 1979; Porrino and Goldman-Rakic, 1982; Morecraft et al., 1992). Our observation that the number of labeled neurons in the hypothalamus was proportional to the size of the injection site was consistent with the findings of Mizuno et al. (1982).

The topographic organization of hypothalamic projections to prefrontal cortices in the monkey had not been addressed previously. We examined the distribution of hypothalamic neurons projecting to limbic versus eulaminate prefrontal cortices, and this approach proved very useful in describing the topography of these connections. We identified differences in the rostrocaudal origin of hypothalamic projections to limbic versus eulaminate prefrontal areas. We also identified mediolateral differences in the topography of hypothalamic projection neurons between orbital and medial limbic areas, but similar topography was not observed for eulaminate cortices. Within specific hypothalamic areas and nuclei (e.g., the LA and DA), the location of projection neurons directed to different prefrontal cortices also varied according to destination.

The present findings concerning hypothalamocortical projection patterns correspond fairly well with those observed in the rat (Divac et al., 1978; McKinney et al., 1983; Vincent et al., 1983; Köhler and Swanson, 1984; Saper, 1985; Vertes et al., 1995). In the rat, three main groups of hypothalamic cells, classified according to neurochemistry and connections, project to the cerebral cortex (for review, see Saper, 1990). Histaminergic tuberomammillary neurons have a diffuse projection to the entire cortex (Köhler et al., 1985; Ericson et al., 1987). Neurons containing

melanin-concentrating hormone (MCH) in the tuberal hypothalamus have a somewhat topographic projection to the cortex (Saper, 1985; Saper et al., 1986; Bittencourt et al., 1992). A third group of neurons in the posterolateral hypothalamus do not contain histamine or MCH, and they have a highly topographic projection to the cortex (Saper, 1985; for review, see Saper, 1990).

In the absence of comparable neurochemical studies in the monkey, it is not possible to determine whether the above projection patterns are also present in the monkey. However, several findings are relevant in this regard. For example, as in the rat, we found that neurons in the TM issued projections to every prefrontal and premotor cortical site included in this study. These projections may correspond to the diffuse histaminergic projections from the TM to the cortex seen in the rat (for review, see Saper, 1990). In contrast to a diffuse projection, we noted that limbic prefrontal cortices received more projections from the tuberal division of the LA than did the best delineated eulaminate prefrontal cortices. The specificity of this projection in the monkey is consistent with the observation that MCH innervation from the tuberal hypothalamus in the rat is strongest to limbic cortices and weakest to primary sensory cortices (Bittencourt et al., 1992). Finally, we observed a tendency for the more lateral prefrontal areas to receive heavier input from the lateral part of the posterior hypothalamus, and the more medial prefrontal areas to receive heavier input from the medial part of the posterior hypothalamus. This observation may reflect the presence of a group of neurons in the posterior hypothalamus of the monkey analogous to the group of posterolateral neurons with a highly topographic cortical projection identified in the rat.

Our analyses enabled us to address several issues concerning how the hypothalamus projects to the prefrontal cortex. First, we sought to answer whether the hypothalamus projects to prefrontal cortex in a nonspecific or specific manner. In the most general analysis, the hypothalamic projections do appear to be nonspecific, with neurons in essentially the same areas terminating in all prefrontal cortices. However, a more in-depth analysis revealed differences in the origin of hypothalamic input targeting eulaminate and limbic prefrontal areas (Fig. 20). Specifically, eulaminate areas received projections from the posterior hypothalamus and were targeted by an equal number of projection neurons from the medial and lateral divisions. Thus, along the mediolateral axis, the hypothalamus seems to project to eulaminate prefrontal cortices in a fairly nonspecific manner. Limbic prefrontal areas, in contrast, received projections from neurons distributed across the rostrocaudal extent of the hypothalamus. Moreover, the distribution of neurons projecting to orbital and medial limbic prefrontal areas differed along the mediolateral axis. These findings suggest that the hypothalamic projections to limbic prefrontal areas are more widespread along the rostrocaudal axis but more focal along the mediolateral axis than those to eulaminate areas and, presumably, reflect their functional relationships with these cortices.

Descending projections from prefrontal cortex to hypothalamus show a greater specificity than reciprocal projections

Unlike the ascending projections (which target lateral, orbital, and medial prefrontal areas), the descending connections from prefrontal cortex to the hypothalamus were more selective. As illustrated in Figure 20, we found that orbital and medial prefrontal areas issued projections to the hypothalamus. In contrast, lateral prefrontal areas appeared to have few, if any, descending projections to the hypothalamus.

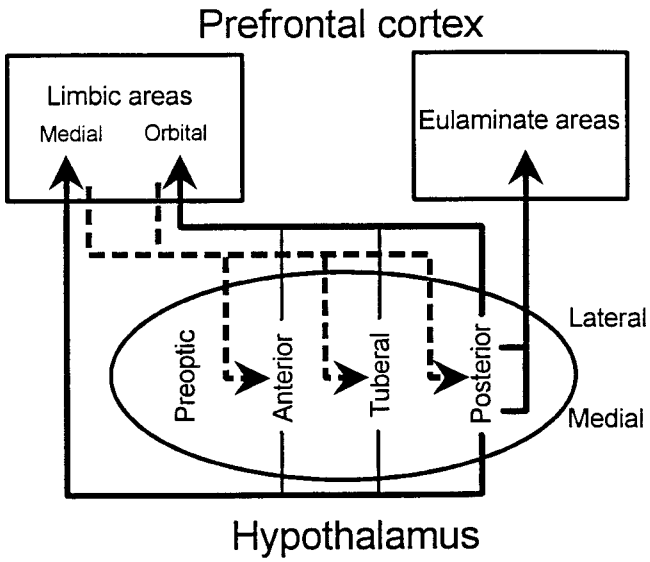


Fig. 20. Schematic diagram of the ascending (solid lines) and descending (dashed lines) connections between prefrontal cortices and the hypothalamus. For simplicity, only the predominant projections are indicated. Eulaminate prefrontal areas receive projections primarily from the posterior hypothalamus. Limbic prefrontal areas receive projections from anterior, tuberal, and posterior hypothalamus (thin lines represent projections from fewer neurons than thick lines); orbital areas receive input from more neurons in the lateral than medial hypothalamic regions and medial areas receive more robust projections from medial than lateral hypothalamic regions. Descending projections to the anterior, tuberal, and posterior hypothalamus arise mostly from the limbic prefrontal areas.

Projections issued from prefrontal areas to the hypothalamus terminated mostly in the posterior hypothalamus, primarily in areas with retrogradely labeled neurons. Anterograde label was also apparent in some areas in the anterior and tuberal hypothalamus. Our findings are consistent with those of previous studies. In monkeys, fiber degeneration studies indicated the presence of descending projections to the hypothalamus from prefrontal areas, particularly the posterior orbital surface (Wall et al., 1951; Nauta, 1962; DeVito and Smith, 1964; Johnson et al., 1968). Johnson et al. (1968) found that lesions of the posterior orbital surface caused heavy anterograde degeneration in the hypothalamus, whereas lesions of the anterior dorsal surface or within the principal sulcus resulted in very little or no degeneration in the hypothalamus.

Our analyses suggest that these findings can be understood, in part, when viewed within the framework of a structural model of the prefrontal cortex that takes into account differences in laminar organization between limbic and eulaminate prefrontal areas (Barbas and Rempel-Clower, 1997). Limbic prefrontal areas (i.e., posterior orbital and medial areas) consistently projected to the hypothalamus, as did the adjacent areas 11 and O12. In contrast, the best delineated eulaminate prefrontal areas (i.e., dorsolateral areas) issued sparse, if any, projections to

the hypothalamus. Projections from orbital and medial prefrontal cortex to the hypothalamus also have been demonstrated using modern tracing methods (Tazawa et al., 1987; Öngür et al., 1996). Our findings are consistent with studies in rats where projections from the insular, infralimbic, and prelimbic areas terminate in essentially the same areas in which we observed terminations from prefrontal limbic areas in the monkey (Kita and Oomura, 1982; Saper, 1982; Wouterlood et al., 1987; Hurley et al., 1991; Yasui et al., 1991; Buchanan et al., 1994).

Specificity of descending and ascending projections

The most dense projections to the hypothalamus originated in prefrontal limbic areas rather than eulaminate cortices. The specificity of these projections was revealed further by our finding that the size of the injection was not positively correlated with the density of anterograde label in the hypothalamus. The location of the injection site—not the size of the injection—seemed to be critical in determining the density of anterograde label. In contrast, the reciprocal ascending projections do not appear to have this degree of specificity, as suggested by the significant correlation between the size of the injection and the number of retrogradely labeled neurons in the hypothalamus. This significant correlation supports the previous reports that the hypothalamus has widespread projections to the cortex (Mesulam et al., 1983; Vincent et al., 1983; Köhler et al., 1985; Saper, 1985; Ericson et al., 1987; Bittencourt et al., 1992). Our data confirm and extend these findings by indicating that although the hypothalamic projections are widespread, they are still topographically organized. Thus, whereas approximately the same overall number of neurons in the hypothalamus project to each area of prefrontal cortex, the specific origin of these projections is related to the particular prefrontal area in which they terminate.

Functional implications

The observed topographical differences of hypothalamic projection neurons directed to limbic and eulaminate prefrontal cortices suggest that these areas may have different functional relationships with the hypothalamus. The most striking difference between the connections of prefrontal limbic and eulaminate cortices with the hypothalamus is that limbic areas, unlike the best delineated eulaminate areas, have descending projections to the hypothalamus (Fig. 20). The projections from prefrontal limbic cortices may account, in part, for the observed autonomic responses elicited by their electrical stimulation in classic studies (Bailey and Sweet, 1940; Smith, 1945; Ward, 1948; Kaada et al., 1949; Cropp and Manning, 1960; Hall and Cornish, 1977; Hall et al., 1977).

There is considerable evidence that prefrontal limbic areas are a site of emotional processing of complex stimuli (for reviews, see Damasio, 1994; Barbas, 1995a), and recent evidence suggests that prefrontal limbic cortices are important for autonomic responses to emotions (Damasio et al., 1990; Bechara et al., 1996). Prefrontal limbic areas have connections with cortices representing each of the sensory modalities and with the amygdala, the thalamus, and the hippocampus that may allow them to integrate the physical attributes of perceptual information with the emotional significance of this information. Projections from prefrontal limbic areas terminate in the LA, the PA, and the Pef, which have autonomic functions and are linked directly with brainstem and spinal cord autonomic nuclei (Saper et al., 1976; Cechetto and Saper, 1988; Allen and Cechetto, 1992; for reviews, see Saper, 1990; Loewy, 1991; Saper, 1995). Thus, prefrontal limbic areas appear to exert direct influence on key autonomic centers in the hypothalamus through descending pathways. Because the cortex is essential for cognitive awareness of the emotive significance of events, initiation of autonomic responses to complex emotional stimuli is likely to require activation of these cortical pathways.

The ascending projections from the hypothalamus to limbic and eulaminate prefrontal areas also suggest functional differences. Eulaminate prefrontal areas receive input primarily from the posterior division of the hypothalamus, and these projections originate in the same general populations of hypothalamic neurons regardless of their destination in the orbital, medial, or lateral prefrontal eulaminate areas. Thus, hypothalamic input to eulaminate prefrontal areas may be of a diffuse nature, similar to the input to other cortical areas, and possibly related to general arousal and wakefulness (Kievit and Kuypers, 1975; Mesulam et al., 1983; Tigges et al., 1983; Vincent et al., 1983; Saper, 1985). The neurochemical characteristics of hypothalamic neurons projecting to cortex support this idea. Many hypothalamic areas with ascending projections to prefrontal areas originate from areas that contain histaminergic neurons, which have widespread projections to almost all areas of the brain and seem to regulate arousal (Köhler et al., 1985; Ericson et al., 1987; Lin et al., 1988; Inagaki et al., 1990; Panula et al., 1990; for review, see Wada et al., 1991). Similarly, many neurons in the tuberal lateral hypothalamus that project to the cortex contain MCH, which also has been suggested to play a role in general arousal and feeding behavior (for review, see Nahon, 1994).

The hypothalamic projections to limbic prefrontal areas are more diverse than those to eulaminate areas, arising in part from the anterior and tuberal divisions in addition to the posterior hypothalamus. The broader distribution of projection neurons terminating in limbic than eulaminate prefrontal areas suggests that the input to the limbic cortices may be of a different functional nature. Our findings that robust descending projections to the hypothalamus arise from limbic areas suggests that limbic prefrontal areas can initiate autonomic responses. In that context, the ascending projections to limbic prefrontal areas may provide feedback from autonomic areas in the hypothalamus for modulating the descending input to hypothalamic autonomic areas.

We also noted differences in the mediolateral origin of hypothalamic projections to specific limbic prefrontal areas (i.e., medial and orbital). Medial and orbital prefrontal areas have important differences in their connections with other areas. For example, the amygdala targets primarily orbitofrontal areas, whereas the hippocampal formation projects most strongly to medial prefrontal cortices (Porrino et al., 1981; Barbas and De Olmos, 1990; Barbas and Blatt, 1995). It seems likely that medial and orbital limbic prefrontal areas receive more specific information from the hypothalamus, related to the different functions of these cortical areas.

In conclusion, our findings suggest that the hypothalamic connections of eulaminate prefrontal areas are similar; they are ascending and largely unidirectional, and

may be associated with general arousal. Prefrontal limbic areas, in contrast, have bidirectional connections with the hypothalamus. Descending projections from prefrontal limbic areas terminate in hypothalamic autonomic areas and may be an important link for autonomic responses to emotion. The ascending projections from the hypothalamus back to limbic prefrontal areas show a mediolateral topography and may allow for cortical modulation of autonomic activation.

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