©1987 The Institute of Mind and Behavior, Inc.
The Journal of Mind and Behavior
Autumn 1987, Volume 8, Number 4
Pages 519 [43]–536 [60]
ISSN 0271–0137
ISBN 0–930195–04–3

GABA-Peptide Neurons of the Primate Cerebral Cortex

Edward G. Jones

University of California, Irvine

The neuropeptide containing neurons of the neocortex do not seem to be a highly heterogeneous group as commonly supposed. Virtually all of the known peptides appear to be contained in a limited type, perhaps a single class, of GABAergic intrinsic neuron. VIP may be more commonly found in a cholinergic neuron that shares the morphological features of the GABA-peptide class. The majority of cortical neurons, including all the pyramidal neurons and spiny intrinsic neurons, amounting to about 75% of the total neuronal population, and most varieties of the 25% GABAergic intrinsic neurons, are not immunoreactive for known peptides. The roles of those peptides, that are apparently co-released with GABA in cortical funtion, are still unknown.

Immunocytochemistry has revealed the existence of a large population of neurons immunoreactive for both gamma-aminobutyric acid (GABA) and its synthesizing enzyme, glutamic acid decarboxylase (GAD), in the cerebral cortex of a range of mammalian species (Bear, Schmechel, and Ebner,1985; Emson and Hunt, 1981; Hendrickson, Hunt, and Wu, 1981; Hendry, Houser, Jones, and Vaughn, 1983; Houser, Hendry, Jones, and Vaughn,1983; Lin, Lu, and Schmechel, 1985; Peters, Proskauer, and Ribak, 1982; Ribak, 1978). Quantitative analysis of the monkey cortex indicates that approximately 25% of the neuronal population in most cortical areas is GABA immunoreactive (Hendry, Schwark, Jones, and Yan, 1987). Probably all the morphological varieties of intrinsic cortical neurons except the population of small, putatively excitatory, dendritic-spine-bearing neurons of layer IV, are GABA immunoreactive (Jones and Hendry, 1986). The several varieties of pyramidal neurons in the cortex are also excitatory and probably use glutamate as their transmitter (Cotman, Foster, and Lanthorn, 1981; Donoghue, Wenthold, and Altschuler, 1985; Streit, 1984).

Neuroactive brain-gut peptides were reported in the mammalian cerebral cortex in radioimmunoassay and immunocytochemical studies beginning in about 1976 (e.g., Carraway and Leeman, 1976; Dockray, 1976; Hökfelt et al.,

---

Personal work was supported by Grant Number NS 21377 from the National Institutes of Health, United States Public Health Service. Requests for reprints should be sent to Edward G. Jones, M.D., Ph.D., Department of Anatomy and Neurobiology, University of California, Irvine, California College of Medicine, Irvine, California 92717.

1976, 1978; Muller, Straus, and Yalow, 1977; Paxinos, Emson, and Cuello, 1978; Sachs, Hökfelt, Meyerson, Elde, and Rehfeld, 1977; Said and Rosenberg, 1976; Straus et al., 1977; Uhl and Snyder, 1976). Twelve or more neuropeptides have now been reported in neurons and/or fibers of the cortex by immunocytochemistry. Table 1 lists the cortical neuropeptides thus far identified and indicates the distribution of cells or fibers showing immunoreactivity for them. Cells immunoreactive for many peptides are widely distributed in all cortical areas; others have a more restricted distribution.

Table 1

Known Neocortical Transmitters and Neuropeptides*

	Extrinsic *(In afferent fibers)*		**Intrinsic** *(In cortical neurons)*	
	General (to all areas)	*Regional* (to some areas)	*General*	*Regional*
GABA	+	–	++++	–
ACh	++	–	++	–
5HT	+++	–	–	–
NA	+++	–	–	–
DA	–	++	–	–
Glu/Asp	(++)	–	(+++)	–
CCK	–	+	+++	–
NPY	–	–	+++	–
SRIF	–	–	+++	–
VIP	–	–	++	–
SP	–	+	+++	–
DYN	–	–	++	–
CRF	–	–	–	+
NT	–	+	–	–
CGRP	–	–	–	+

()Likely, not proven conclusively.

* From Jones and Hendry, 1986. Reprinted with permission of *Trends in Neuroscience*, 9, 71–76, © 1986 Elsevier Science Publishers B.V., Amsterdam.

The large number of cortical peptides and the wide distribution of cells immunoreactive for them have led many workers to attempt to place the considerable variety of peptide immunoreactive cortical cells in different morphological categories: bi-polar, multipolar, bi-tufted, etc. (Emson and Hunt, 1985; McDonald, Parnavelas, Karamanlidis, and Brecha, 1982, 1983; McDonald, Parnavelas, Karamanlidis, Brecha, and Koenig, 1982; McDonald, Parnavelas, Karamanlidis, Brecha, and Rosenquist, 1982; McGinty, van der Kooy, and Bloom, 1984; Morrison, Benoit, Magistretti, and Bloom, 1984; Peters, Miller, and Kimerer, 1983). In our studies of somatostatin (SRIF)-and neuropeptide Y (NPY)-immunoreactive cortical cells (Hendry, Jones, and Emson, 1984) we noted that the cells have a wide variety of dendritic field

configurations when only the usual immunocytochemical staining of the proximal dendrites is considered. When more complete staining was achieved, all NPY and SRIF immunoreactive cells, irrespective of the arrangements of their proximal dendrites, extended elongated vertical processes through several layers of the cortex. Studies of cortical cells immunoreactive for other neuropeptides (Hendry, Jones, and Emson, 1984; Jones and Hendry, 1986), and a review of the literature, have led us to conclude that all the known cortical neuropeptides are contained in a limited cell class that can best be described as having a small rounded soma and a variable number of vertical processes (see Figure 1). This particular cell type is usually also GABA and GAD immunoreactive.

The cortical cells immunoreactive for known neuropeptides may also show co-localization of immunoreactivity for other classical neurotransmitters or their biosynthetic enzymes such as choline acetyltransferase. Eckenstein and Baughman (1984) in the rat cortex identified cells showing co-localization of immunoreactivity for vasoactive intestinal polypeptide (VIP) and choline acetyltransferase (ChAT). At the same time Schmechel, Vickrey, Fitzpatrick, and Elde (1984) reported co-localization of SRIF and GAD immunoreactivity in the rat, cat and monkey cortex; Somogyi et al. (1984) identified cells immunoreactive for SRIF and GABA or for CCK and GABA in the cat cortex and hippocampus; and Hendry, Jones, DeFelipe et al. (1984) identified cells immunoreactive for SRIF and GAD, CCK and GAD or NPY and GAD in the monkey and cat cortex and showed that at least 95% of cells immunoreactive for any of these peptides was also immunoreactive for GAD. Most SRIF

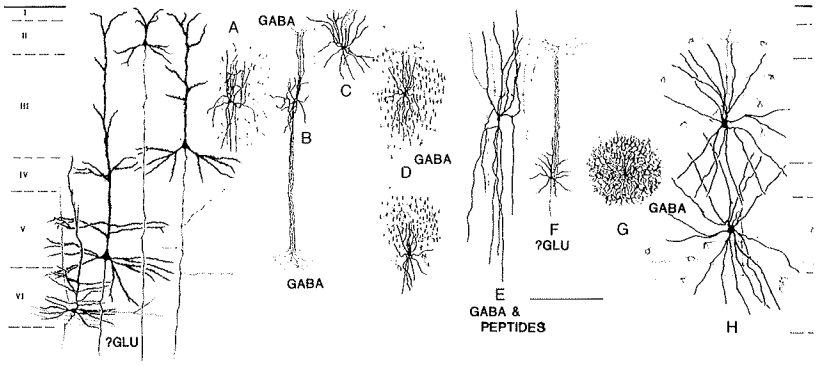

Figure 1: Morphological types of cells identifiable in monkey cerebral cortex, based on studies of Jones (1984) on sensory-motor areas. Cells at left are typical pyramidal cells of layers II-IV which are likely to use glutamate as a transmitter. Cells A-H are intrinsic neurons. All except the small spiny, putatively excitatory cell (F) of layer IV are proven or likely to be GABAergic. Long, stringy cell (E) is a typical cell type that co-localizes GABA and neuropeptides or (in rat) acetylcholine and neuropeptides. A: cell with axonal arcades; B: double bouquet cell; C, H: basket cells; D: chandelier cells; G: neurogliaform cell. Bar 100 μm.

positive cells in monkey cortex are also NPY positive (Hendry, Jones, and Emson, 1984) and several other cortical peptides are almost invariably co-localized with GABA and/or GAD (Jones and Hendry, 1986; Jones et al., 1987). The characteristic morphology of the peptidergic neurons of the cortex, their content of more than one peptide and their almost invariable co-localization of a classical transmitter thus make them a unique group. The purpose of the present study is to quantify the numbers and distributions of GABA neurons as a whole and to show where the peptide producing GABA neurons fit into this group.

The Proportion of GABAergic Cortical Neurons

Sections of the monkey cortex stained immunocytochemically for GABA or GAD reveal a large proportion of neurons immunoreactive for these compounds (see Figure 2). Stained cells appear in all layers of all areas, with higher concentrations in the middle layers, particularly layer IV. By preparing tissue in a manner that maximizes penetration of and staining by the immunoreagents, it is possible to count accurately the GABAergic cell population from area to area (Hendry et al., 1987). In cynomolgus monkeys, counts have been made in 50 micron wide vertical columns extending from pia mater to the white matter across ten areas of the cortex: areas 17 and 18 of the visual cortex, the somatosensory and motor fields (areas 4, 3b, 1 and 2), the parietal fields areas 5 and 7, the temporal field area 21 and the medial and lateral frontal cortex (see Table 2). With the exception of area 17, these counts reveal a remarkable constancy of GABA immunoreactive cell numbers from area to area. All areas except area 17 average approximately 38 to 40 GABA or GAD immunoreactive cells per 50 micron wide traverse. In area 17 the number is approximately 58 to 60. When these numbers are compared, either with our own counts of the total, Nissl-stained neuronal population (Table 2) or with the counts made by Rockel, Hiorns, and Powell (1980) in rhesus monkeys, it is apparent that GABAergic neurons form approximately 25% of the cell population in any area except the visual—in which, despite a large increase in the GABA population, the total cell population increasing by more than the 100% causes GABA population to fall to approximately 20%.

Varieties of Cortical GABA Neuron

Among the large cortical GABAergic population, there are a variety of morphological types of neuron (Jones, 1984) (Figure 1). All are nonpyramidal and lack significant populations of dendritic spines; all their axons are intrinsic to the cortex and form symmetrical synaptic contacts with flattened synaptic vesicles (Hendry, Houser et al., 1983). All are, thus, typical non-spiny types of cortical interneuron. The dendritic fields of other GABA immunoreactive

neurons, so far as the fields can be stained (Houser, Hendry, Jones, and Vaughn, 1983), suggest that possibly all of the six or so types of non-spiny cortical intrinsic neuron are GABAergic. Among the non-spiny forms of cortical

Figure 2: GABA-immunoreactive neurons distributed through all layers of the monkey visual cortex in a 10 μm thick section. Bar 250 μm.

Table 2

Mean Number (±SD) of GABA-immunoreactive Neurons and of all Thionin-stained Neurons per 50-μm-wide Column Through the Thickness of Areas 4, 3b, 1–2, 5, 7, 18, and 17 of Monkey Cortex.

	CM 181			CM 187		
Area	GABA	Total	%	GABA	Total	%
4	39.0 ± 2.9	158.9 ± 16.1	24.5 ± 2.0	39.4 ± 2.7	159.4 ± 16.3	24.5 ± 1.3
3b	39.9 ± 2.8	152.7 ± 11.9	26.1 ± 1.7	32.1 ± 5.9	154.9 ± 11.7	20.6 ± 1.2
1–2	40.1 ± 2.6	154.8 ± 14.2	25.9 ± 1.8	38.4 ± 4.0	157.9 ± 16.1	24.4 ± 2.1
5	40.4 ± 2.2	163.1 ± 10.6	24.7 ± 2.3	39.2 ± 2.0	160.6 ± 14.1	24.4 ± 1.9
7	38.4 ± 2.9	158.2 ± 9.4	24.1 ± 1.6	40.7 ± 3.7	158.8 ± 14.8	25.1 ± 1.4
18	38.1 ± 2.9	157.3 ± 10.1	24.4 ± 2.1	38.6 ± 3.6	157.9 ± 15.0	24.7 ± 2.1
17	59.1 ± 5.7	315.7 ± 19.4	18.7 ± 2.1	58.2 ± 5.7	309.9 ± 22.7	19.2 ± 2.0
	CM 183			CM 189		
Area	GABA	Total	%	GABA	Total	%
4	40.4 ± 3.9	161.7 ± 15.3	25.0 ± 1.7	39.4 ± 2.4	161.6 ± 17.0	24.3 ± 2.1
3b	33.1 ± 5.0	157.9 ± 12.2	21.0 ± 2.1	40.1 ± 3.0	156.5 ± 12.7	25.6 ± 2.3
1–2	38.0 ± 3.3	154.3 ± 11.6	24.6 ± 2.3	38.4 ± 3.3	158.8 ± 11.9	24.0 ± 1.9
5	39.1 ± 2.7	155.3 ± 9.4	25.2 ± 1.8	38.5 ± 3.4	155.1 ± 12.0	24.9 ± 2.0
7	39.9 ± 2.9	157.6 ± 11.8	25.3 ± 1.3	40.4 ± 2.4	160.1 ± 16.5	25.2 ± 2.4
18	38.4 ± 3.9	152.0 ± 9.1	25.3 ± 1.6	38.1 ± 2.9	157.5 ± 17.5	24.2 ± 1.7
17	61.1 ± 4.7	309.8 ± 17.1	19.6 ± 1.5	59.1 ± 5.7	321.3 ± 23.6	18.5 ± 2.2
	CM 184					
Area	GABA	Total	%			
4	40.7 ± 3.4	157.1 ± 15.5	25.2 ± 1.1			
3b	32.9 ± 5.7	160.4 ± 11.0	20.2 ± 1.9			
1–2	40.1 ± 3.1	154.9 ± 9.7	25.1 ± 1.7			
5	40.4 ± 2.0	158.1 ± 13.0	24.9 ± 1.3			
7	40.7 ± 2.8	159.9 ± 11.7	24.3 ± 2.0			
18	40.8 ± 5.0	158.4 ± 16.2	24.7 ± 1.8			
17	60.3 ± 5.3	319.6 ± 21.4	19.1 ± 1.0			

Counts of GABA-positive neurons and of all neurons were made at a magnification of 1250 from adjacent sections, and the percentages of GABA cells were calculated from the quotient of the two values. From Hendry et al. (1987). Reprinted from permission of *Journal of Neuroscience*, 7, 1503–1519, ©1987, The Society of Neuroscience.

interneuron, two at least are certainly GABAergic: the basket cells and the chandelier cells, recognizable because of their unique morphologies. Among the other types are those with small rounded somata from which long thin vertical dendrites arise singly or in tufts, giving the cell a bipolar or bitufted appearance (Figures 1, 3). The somata of these cells appear to be most common in layer II and the superficial part of layer III, and at the junction of layer VI and the white matter. It appears there is reason to believe that this GABAergic cell

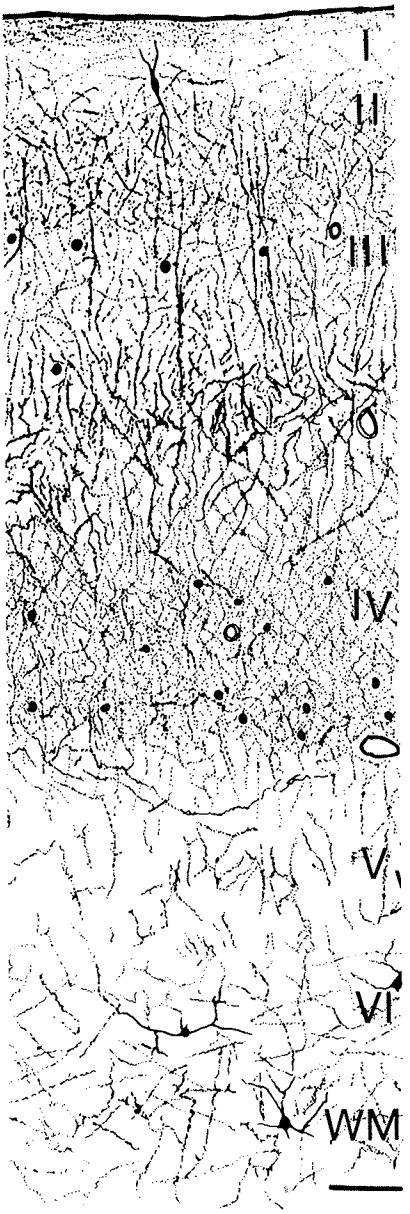

Figure 3: Camera lucida drawing of substance P immunoreactive cells and fibers in deeper layers of monkey visual cortex. Cells without stained processes in layer V co-localize GABA immunoreactivity; cells with long stained processes in layer VI and white matter co-localize NPY immunoreactivity. Bar 100 μm.

type is the cortical cell type that contains all or most of the known cortical neuropeptides.

The laminar concentrations of the somata of these elongated GABA cells correlate quite well with the positions in most cortical areas of the monkey of two strata of somata that are specifically labeled by transport of [^{3}H] GABA injected into superficial or deep cortical layers (DeFelipe and Jones, 1985; Somogyi, Cowey, Halász, and Freund, 1981). When [^{3}H] GABA is injected into layer II and the superficial part of layer III, small non-pyramidal cell somata are labeled in layers V and VI in a small focus immediately deep to the injection focus. Conversely, injection of [^{3}H] GABA into layers V and VI leads to somal labeling in a focus in layer II and the superficial part of layer III, without somal labeling in intervening layers.

This remarkably specific, columnar pattern of interlaminar labeling appears to be based upon high affinity terminal uptake and retrograde axoplasmic transport of [^{3}H] GABA to the somata of cells whose axons interconnect layers II-III with V-VI, and vice versa. Electron microscopic examination shows that cells with vertical dendrites as well as vertical axons appear to be involved in the phenomenon, and somal labeling may be due to a combination of retrograde axonal and dendritic transport. The elongated GABA neurons of layers II-III and V-VI are obvious candidates to form the basis for this specific translaminar transport of [^{3}H] GABA. Their morphology is appropriate, and the transmitter specific retrograde labeling is probably an indication that the neurons use GABA normally (see Streit, 1984).

Cortical Neuropeptide Neurons

The neuropeptides that have been localized by immunocytochemistry in neuronal somata of the cerebral cortex in a number of mammalian species are listed in Table 1. Immunoreactivity for all of those indicated has been observed in the rat and while not all have been localized in the higher primate cortex, there is evidence from radioimmunoassay for the presence of most of them in monkeys and humans.

In monkeys, cats and rats all cells immunoreactive for any of the cortical neuropeptides have an overall similarity in their morphology. We assume, therefore that when cells immunoreactive for peptides hitherto not stained in the primate cortex are revealed, they will resemble their counterparts in other species and the cells immunoreactive for other peptides in the primate cortex.

All cortical neuropeptide cells have small rounded somata found in all layers but with concentrations in layer II and the superficial part of layer III and in layer VI and the immediately underlying white matter (see Figure 3), particularly in monkeys and humans. In some areas additional concentrations of somata can sometimes be found in other layers. In the monkey visual cortex, for example, a significant concentration of SP immunoreactive somata occurs in layer IV as well (Figure 3). The cells, when only the proximal portions of the dendrites are stained, may appear to adopt a variety of shapes and in the

literature are often described variously as bipolar, bi-tufted, multipolar, stellate, etc., and even as pyramidal cells. However, verticality of dendrites is common to all of these cells. Irrespective of the number of dendrites arising from a soma and irrespective of their angles of orgin, all form vertical sets of processes that traverse two or more layers of the cortex perpendicularly. The terminal portions of the processes can branch relatively profusely and tend to set up two major plexuses, one in the supragranular layers and one in the infragranular layers and underlying white matter (Figure 3). Layer IV in some areas is notably devoid of a peptidergic plexus, though in others a third subsidiary plexus may be set up there, especially in area 17 (Figure 3).

The intracortical terminals of all peptidergic neuronal processes are very similar. All contain synaptic vesicles that flatten or become pleomorphic in the usual fixatives, and the vast majority, irrespective of the peptide localized, make symmetric membrane contacts. In these features they closely resemble the terminals of GABA neurons. Contacts are made on large and small dendrites of both pyramidal and non-pyramidal neurons and on dendritic spines. The peptide immunoreactive cells themselves, including those in the white matter beneath the cortex, receive modest numbers of other, usually non-peptidergic synapses.

Co-localization of GABA and Peptides

In the monkey, it has become evident that the population of neurons co-localizing GABA and/or GAD with neuropeptides is particularly high. Virtually all CCK neurons are also GABA and GAD immunoreactive. In the rat, some cells also show VIP immunoreactivity. Approximately 95% of NPY neurons and 95% of SRIF neurons co-localize GABA and GAD. Virtually 100% of SRIF neurons also co-localize NPY and vice versa. Also, 90-95% of SP neurons (100% of those in layer VI) co-localize SRIF and NPY (see Figure 4 and Table 3).

Table 3

Combinations of GABA and Neuropeptide Immunoreactivity Demonstrated to Date in Neocortex

PEPTIDE	%GABA/GAD	% NON-GABA
CCK	100	0
SRIF*	95-97	3-5
NPY*	95-97	3-5
SP		
Small (80%)	100	0
Large* (20%)	10-15	85-90

* SRIF in 100% of NPY cells and NPY in 100% of large SP cells. From Jones and Hendry (1986). Reprinted with permission of Elsevier Science Publishers B.V. (Biomedical Division), Amsterdam © 1986.

Hence, not only are most of the neurons immunoreactive for the peptides studied to date also GABAergic but they often contain other peptides. It is not known yet if the peptides such as dynorphin, hitherto not stained in the monkey cortex, are also contained in GABA neurons. However, cortical cells immunoreactive for these other peptides in rats are morphologically very similar to those that show co-localization of peptide and GABA immunoreactivity in the monkey. Acetylcholine is also co-localized with peptides. Its synthetic enzyme, choline acetyltransferase (ChAT), is co-

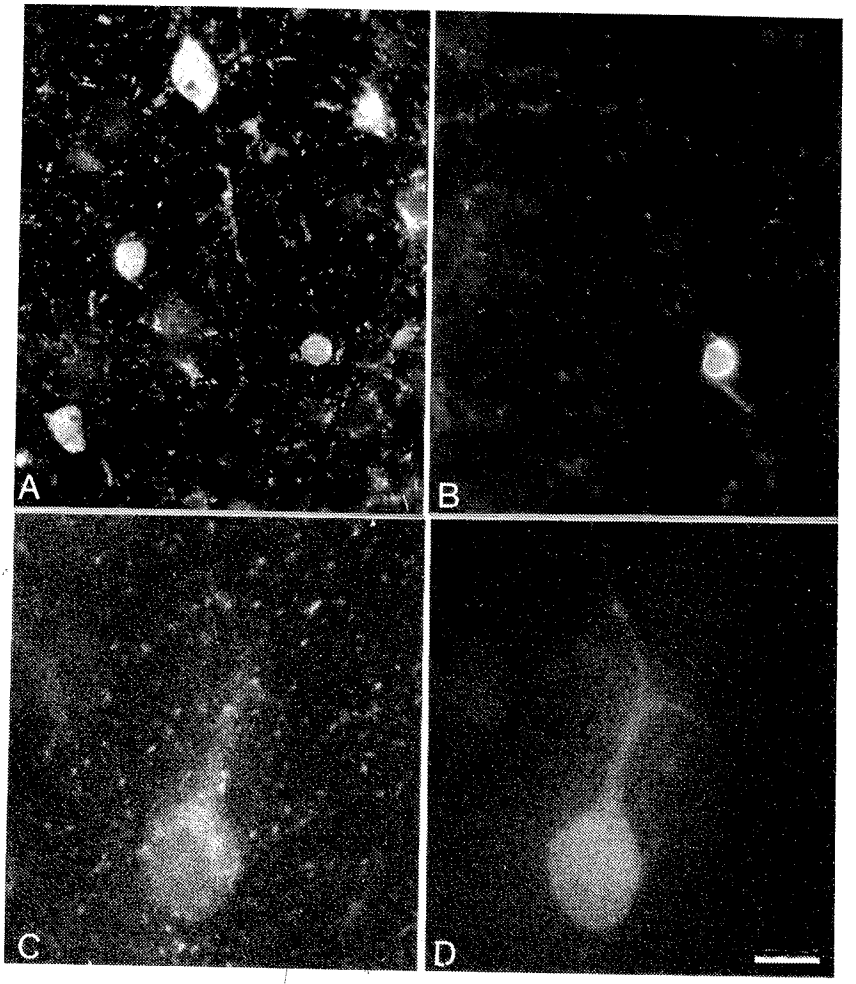

Figure 4: Pairs of fluorescence photomicrographs from sections of monkey cortex stained immunocytochemically for GABA and cholecystokinin. Only one of the GABA immunoreactive cells in A is also immunoreactive for the peptide (B). Bar 30 μm (A, B), 5 μm (C, D).

localized with VIP in an unspecified number of neurons in the rat cortex (Eckenstein and Baughman, 1984). The ChAT immunoreactive cells have the long, stringy morphology typical of peptidergic cells throughout the cortex (Houser et al., 1983, 1985). Whether GAD and ChAT are co-localized in VIP neurons remains to be determined.

Non-peptidergic GABA Neurons

Approximately 70-75% of the GABA positive neurons in monkey cortex do not co-stain for a known peptide. At least two classes of GABA neuron are ruled out as staining for a known peptide on morphology alone. The basket cells cannot be peptide-immunoreactive since no somata larger than 10 microns are stained for known peptides. Basket cells in monkeys normally have somata 20-50 microns in diameter (DeFelipe, Hendry, and Jones, 1986). Chandelier cells are also ruled out, for no chains of peptide immunoreactive axon terminals have ever been demonstrated on the initial segments of pyramidal cell axons where chandelier axons terminate. The small size and elongated morphology of all the peptide neurons thus far identified appears to place them best among a limited cell class. In Golgi preparations, the cell type would be described as bipolar or bi-tufted (Figure 1).

Activity Dependent Regulation of GABA and SP

Synaptic activity can regulate levels of transmitters, transmitter synthesizing enzymes, receptors and the abundance of related mRNAs in the peripheral nervous system (Black et al., 1984; Black, Chkaraishi, and Lewis, 1985; Ip and Zigmond, 1984; Roach, Adler, Krause, and Black, 1985). Comparable effects may be operational in the central nervous system: in the visual cortex of monkeys subjected to monocular visual deprivation for 9-11 weeks, or uniocular injections of tetrodotoxin for 2 weeks, we found that immunoreactive staining for GABA, GAD and SP declines markedly in deprived ocular dominance columns (see Figures 5,6 and 7)(Hendry and Jones, 1986; Hendry et al., 1987). The reduction in staining is due to a reduction both in the number of stained cells and in the neuropil staining in comparison with adjacent non-deprived columns and is quickly reversible after restoration of normal vision. Thus, GABA levels can be down-regulated through a reduction in immunoreactive GAD, and sensory experience also appears to control levels of one peptide expressed by the same cells. Our results show further that levels of immunoreactivity for a calcium/calmodulin dependent protein kinase, CaM Kinase II (Bennett, Erondu, and Kennedy, 1983; Browning, Huganir, and Greengard, 1985; DeRiemer et al., 1984), are actually up-regulated in the deprived cells (Hendry, Jones, and Kennedy,1985; Hendry and Kennedy, 1986), suggesting that the GABA-GAD-SP effect may be mediated by second

messengers associated with changes in intracellular phosphoproteins (Berridge and Irvine, 1984; Nestler, Walaas, and Greengard, 1984; Nishizuka, 1984).

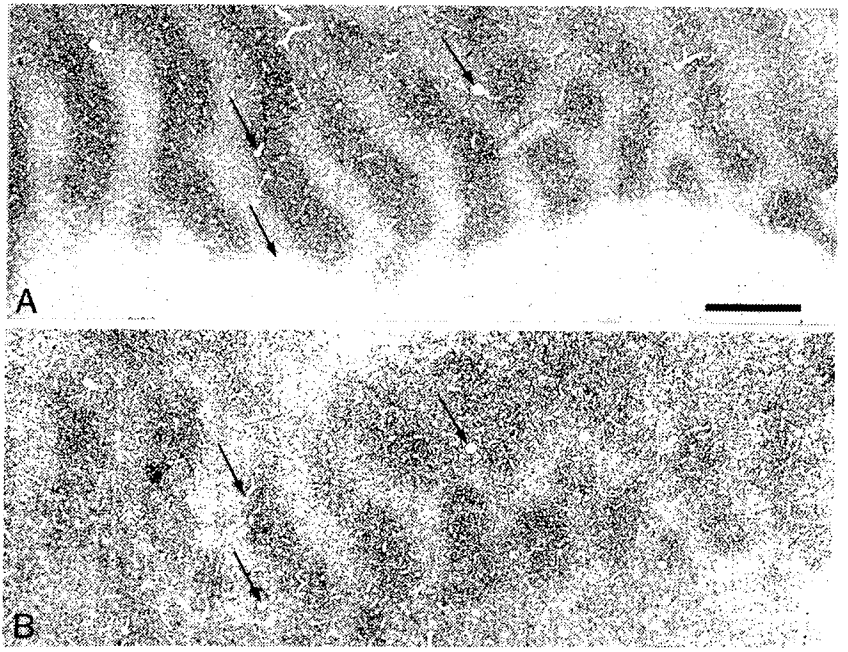

Figure 5: Pair of alternate sections from the visuall cortex of an adult monkey subjected to monocular deprivation for 11 weeks. The same blood vessels are indicated in each pair. Tangential sections through layer IV showing cytochrome oxidase staining (A) and GAD immunoreactivity (B) reduced in deprived ocular dominance strips. Bar 1 mm. From Hendry and Jones, 1986. Reprinted with the permission of *Nature*, 320, 750–753, © 1986 Macmillan Journals Ltd., London.

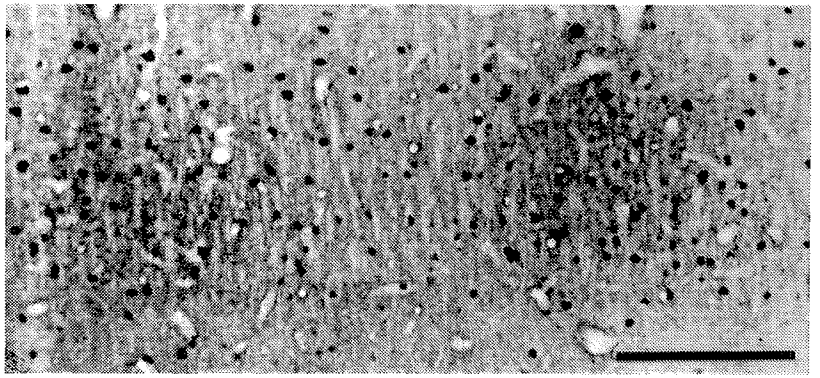

Figure 6: Reduction of GABA immunoreactivity in affected layer IV columns of a monocularly deprived adult monkey. Bar 0.5 mm.

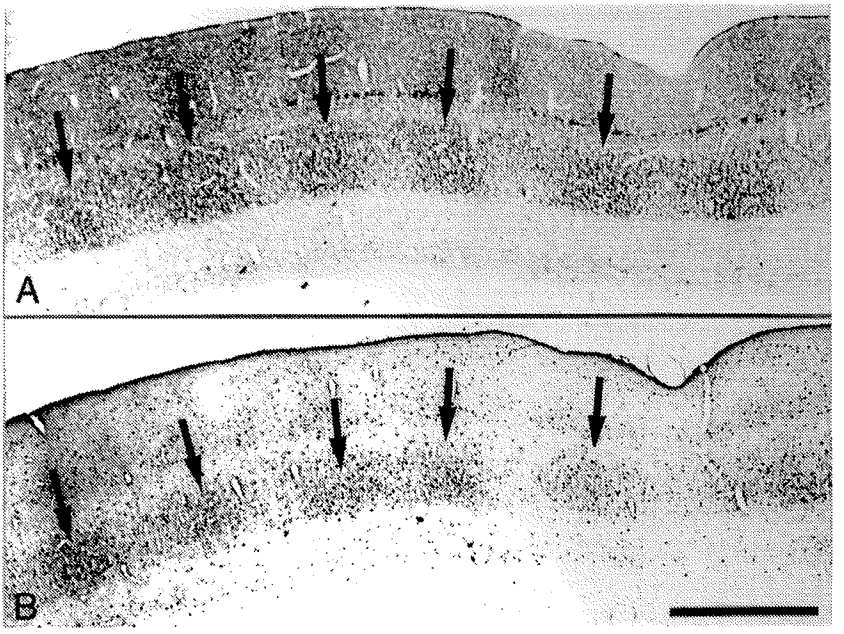

Figure 7: Reduction of cytochrome oxidase staining (A) and SP immunoreactivity (B) in deprived eye dominance columns of an adult monkey. Columns related to undeprived eye are indicated by arrows. Bar 0.5 mm.

Different Classes of GABA-Peptide Cortical Neurons

Division of the peptide immunoreactive neurons of the neocortex into classes on morphological grounds is unreliable, but there appear to be classes that can be distinguished either by the types of peptides they contain or by the synaptic targets of their axons. Most cortical SRIF neurons co-localize NPY and many also contain SP. However, neither of these appears to show CCK or VIP immunoreactivity. All SP cells in layer IVC of the visual area co-localize GABA and not NPY but the layer VI-white matter population co-localizes NPY and not GABA. Other combinations are seen in Table 3. These various combinations could simply reflect the presence of a population of GABA neurons in which all the known cortical peptides are potentially present, but in amounts not normally detectable immunocytochemically. This seems unlikely since certain combinations, e.g., CCK and/or VIP with NPY and/or SRIF, have not been found. Possibly this is correlated with the tendency for CCK and VIP cells to have fewer vertical processes than NPY and SRIF cells.

Differential distributions of their synaptic terminals may be a method of distinguishing classes of cortical peptidergic neurons. Preliminary evidence suggests that most SRIF and NPY immunoreactive synapses are formed on

distal dendritic branches and on dendritic spines of pyramidal neurons. CCK and VIP immunoreactive synapses, by contrast, appear to terminate on more proximal dendrites of pyramidal neurons (Hendry, Jones, and Beinfeld, 1983; Hendry, Jones, and Emson,1984). SP immunoreactive synapses are found at all three sites. Hence the peptidergic cortical neurons may be identifiable along connectional lines that probably have more functional significance than morphology alone.

The Functions of Cortical GABA-peptide Neurons

When most of the cortical neuropeptides are iontophoresed onto neocortical or hippocampal neurons, they usually result in an increase in resting levels of discharge and induce excitatory postsynaptic potentials, with accompanying changes in membrane conductance. The responses can be almost as rapid as those induced by potent excitatory agents such as aspartate or glutamate. Inhibition and complex mixed effects have also been reported, especially with SRIF.

It is hard to explain how the release of peptides from a GABAergic terminal might induce excitation in a postsynaptic cell without postulating special types of mechanisms. Peptides released from a GABAergic synapse could, for example, act back on receptors located on the terminal from which they are released and thus might possibly regulate GABA release. Opioid peptides, acting through receptors located on presynaptic terminals, can inhibit the release of catecholamines, acetylcholine and other peptides (Bloom, 1983), and NPY acts presynaptically in reducing orthodromically induced population spikes in hippocampal neurons (Colmers, Lukowiak, and Pitman, 1985).

Peptides released from GABA terminals might also exert their effects over wide distances, perhaps on receptors and on populations of neurons far removed from the release site. Populations of neurons in amphibian sympathetic ganglia appear to be affected in this way by a luteinizing hormone releasing hormone-like peptide co-released with acetylcholine (Jan and Jan, 1982).

Other potential actions of neuropeptides in the cerebral cortex include the regulation of vascular pefusion and trophic effects. NPY and VIP are strongly vasoactive (Edvinsson, 1985) and VIP co-released with acetylcholine from parasympathetic terminals in the submandibular gland, leads to vasodilatation, increased blood flow and, thus, to enhancement of the secretomotor effect of ACh (Lundberg et al., 1980). NPY is a vasoconstrictor and, thus, the two together might be effective in the control of cortical vascular perfusion (McCulloch, 1983), perhaps activity mediated.

SP, VIP and vasopressin also stimulate DNA synthesis and mitogenesis in mesodermal cells and in cultured cell lines (Brenneman, Eider, and Seigel, 1984; James and Bradshaw, 1984; Nilsson, von Euler, and Dalsgaard, 1985). Some of

the polypeptide growth factors also contain amino acid sequences closely similar to those of known neuropeptides (Gimenez-Gallego et al., 1985). In the peripheral nervous system certain neuropeptides such as VIP and secretin seem to be capable of inducing tyrosine hydroxylase in sympathetic postganglionic neurons (Ip, Ho, and Zigmond, 1982; Ip and Zigmond, 1984). Hence, long-term modulations of nerve cell chemistry may be one of the more important functions of the peptides.

In the neocortex, levels of certain peptides are altered in demented states. SRIF levels decline in the cortex of cases of Alzheimer's disease (Davies, Katzman, and Terry, 1980; Rosser et al., 1980) and SRIF falls in the frontal cortex of Parkinsonian patients with dementia. In Alzheimer's disease there is also a large decrease in markers for acetylcholine but no decline in those for GABA with which SRIF is normally co-localized. The latter suggests a differential regulation of GABA and the peptide in this disease.

References

Bear, M. F., Schmechel, D. E., and Ebner, F. F. (1985). Glutamic acid decarboxylase in the striate cortex of normal and monocularly deprived kittens. *Journal of Neuroscience*, *5*, 1262–1275.

Bennett, M. K., Erondu, N. E., and Kennedy, M. B. (1983). Purification and characterization of a calmodulin-dependent protein kinase that is highly concentrated in brain. *Journal of Biological Chemistry*, *258*,12735–12744.

Berridge, M. J., and Irvine, R. F. (1984). Inositol triphosphate, a novel second messenger in cellular signal-transduction. *Nature*, *312*, 315–321.

Black, I. B., Adler, J. E., Dreyfus, C. F., Jonakait, G. M., Katz, D. M., LaGamma, E. F., and Markey, K. M. (1984). Neurotransmitter plasticity at the molecular level. *Science*, *225*, 1266–1270.

Black, I. B., Chkaraishi, D. M., and Lewis, E. J. (1985). Trans-synaptic increase in RNA coding fortyrosine hydroxylase in a rat sympathetic ganglion. *Brain Research*, *339*, 151–153.

Bloom, F. E. (1983). The endorphins: A growing family of pharmacologically pertinent peptides. *Annual Review of Pharmacology and Toxicology*, *231*, 151–170.

Brenneman, D. E., Eider, L. E., and Seigel, R. E. (1984). Vasoactive intestinal peptide increases activity-dependent neuronal survival in developing spinal cord cultures. *Neuroscience Abstracts*, *10*, 1050.

Browning, M. D., Huganir, R., and Greengard, P. (1985). Protein phosphorylation and neuronal function. *Journal of Neurochemistry*, *45*, 11–23.

Carraway, R., and Leeman, S. E. (1976). Characterization of radioimmunoassayable neurotensin in the rat. *Journal of Biological Chemistry*, *251*, 1045–1052.

Colmers, W. F., Lukowiak, K., and Pitman, Q. J. (1985). Neuropeptide Y reduces orthodromically evoked population spike in rat hippocampal CA1 by a possibly presynaptic mechanism. *Brain Research*, *346*, 404–408.

Cotman, C.W., Foster, A., and Lanthorn, T. (1981). An overview of glutamate as a neurotransmitter. In G. DiChiara and G. L. Gessa (Eds.), *Advances in biochemical psychopharmacology, Vol. 27, Glutamate as a neurotransmitter* (pp.1–27). New York: Raven Press.

Davies, P., Katzman, R., and Terry, R. (1980). Reduced somatostatin-like immunoreactivity in cerebral cortex from cases of Alzheimer's disease and Alzheimer senile dementia. *Nature, London*, *288*, 279–280.

DeFelipe, J., Hendry, S. H. C., and Jones, E. G. (1986). A correlative electron microscopic study of basket cells and large GABAergic neurons in the monkey sensory-motor cortex. *Neuroscience*, *17*, 991–1009.

DeFelipe, J., and Jones, E. G. (1985). Vertical organization of γ-aminobutyric acid-accumulating intrinsic neuronal systems in monkey cerebral cortex. *Journal of Neuroscience*, *5*, 3246–3260.

DeRiemer, S. A., Kaczmarek, L. K., Lai, Y., McGuiness, T. L., and Greengard, P. (1984). Calcium/calmodulin-dependent protein phosphorylation in the nervous system of aplysia. *Journal of Neuroscience, 4*, 1618–1625.

Dockray, G. J. (1976). Immunochemical evidence of cholecystokinin-like peptides in brain. *Nature, London, 264*, 568–570.

Donoghue, J. P., Wenthold, R. J., and Altschuler, R. A. (1985). Localization of glutaminase-like and aspartate aminotransferase-like immunoreactivity in neurons of cerebral neocortex. *Journal of Neuroscience, 5*, 597–2609.

Eckenstein, F., and Baughman, R. W. (1984). Two types of cholinergic innervation in cortex, one co-localized with vasoactive intestinal polypeptide. *Nature, 314*, 153–155.

Edvinsson, L. (1985). Functional role of perivascular peptides in the control of cerebral circulation. *Trends in Neuroscience, 8*, 126–131.

Emson, P. C., and Hunt, S. P. (1981). Anatomical chemistry of the cerebral cortex. In F. O. Schmitt, F. C. Worden, G. Adelman, and S. G. Dennis (Eds.), *The organization of the cerebral cortex* (pp. 325–345). Cambridge, Massachusetts: MIT Press.

Emson, P. C., and Hunt. S. P. (1985). Peptide-containing neurons of the cerebral cortex. In E. G. Jones and A. Peters (Eds.), *Cerebral cortex, Vol. 2, Functional properties of cortical cells* (pp. 145–172). New York: Plenum Press.

Gimenez-Gallego, G., Rodkey, J., Bennett, C., Rios-Candelore, M., DeSalvo, J., and Thomas, K. (1985). Brain-derived acidic fibroblast growth factor: Complete amino acid sequence and homologies. *Science, 230*, 1385–1388.

Hendrickson, A. E., Hunt, S. P., and Wu, J. -Y. (1981). Immunocytochemical localization of glutamic acid decarboxylase in monkey striate cortex. *Nature, London, 292*, 605–606.

Hendry, S. H. C., Houser, C. R., Jones, E. G., and Vaughn, J. E. (1983). Synaptic organization of immunocytochemically identified GABA neurons in monkey sensory-motor cortex. *Journal of Neurocytology, 12*, 639–660.

Hendry, S. H. C., and Jones, E. G. (1986). Reduction in number of immunostained GABA neurons in deprived-eye dominance columns of monkey area 17. *Nature, 320*, 750–753.

Hendry, S. H. C., Jones, E. G., and Beinfeld, M. C. (1983). Cholecystokinin-immunoreactive neurons in rat and monkey cerebral cortex make symmetric synapses and have intimate associations with blood vessels. *Proceedings of the National Academy of Sciences USA, 80*, 2400–2404.

Hendry, S. H. C., Jones, E. G., DeFelipe, J., Schmechel, D., Brandon, C., and Emson, P. C. (1984). Neuropeptide containing neurons of the cerebral cortex are also GABAergic. *Proceedings of the National Academy of Sciences USA, 81*, 6526–6530.

Hendry, S. H. C., Jones, E. G., and Emson, P. C. (1984). Morphology, distribution and synaptic relations of somatostatin- and neuropeptide y-immunoreactive neurons in rat and monkey neocortex. *Journal of Neuroscience, 4*, 2497–2517.

Hendry, S. H. C., Jones, E. G., and Kennedy, M. B. (1985). Modulation of GABA, substance P and protein kinase immunoreactivities in monkey striate cortex following eye removal. *Neuroscience Abstracts, 11*, 16.

Hendry, S. H. C., and Kennedy, M. B. (1986). Altered immunoreactivity for a calcium/calmodulin-dependent kinase in neurons of monkey striate cortex deprived of visual input. *Proceedings of the National Academy of Sciences USA, 83*, 1536–1540.

Hendry, S. H. C., Schwark, H. D., Jones, E. G., and Yan, J. (1987). Numbers and proportions of GABA immunoreactive neurons in different areas of monkey cerebral cortex. *Journal of Neuroscience, 7*, 1503–1519.

Hökfelt, T., Elde, R., Johansson, O. (1978). Distribution of peptide-containing neurones. In M. A. Lipton, A. Dimascio, and K. F. Killam (Eds.), *Psychopharmacology: A generation of progress* (pp. 39–66). New York: Raven Press.

Hökfelt, T., Meyerson, B., Nilsson, G., Pernow, B., and Sachs, C. (1976). Immunohistochemical evidence for substance P containing nerve endings in the human cortex. *Brain Research, 104*, 181–186.

Houser, C. R., Crawford, C. D., Barber, R. P., Salvaterra, P. M., and Vaughn, J. E. (1983). Organization and morphological characteristics of cholinergic neurons: An immunocytochemical study with a monoclonal antibody to choline acetyltransferase. *Brain Research, 266*, 97–119.

Houser, C. R., Crawford, G. D., Salvaterra, P. M., and Vaughn, J. E. (1985). Immunocytochemical localization of choline acetyltransferase in rat cerebral cortex: A study of cholinergic neurons and synapses. *Journal of Comparative Neurology, 234*, 17–33.

Houser, C. R., Hendry, S. H. C., Jones, E. G., and Vaughn, J. E. (1983). Morphological diversity of immunocytochemically identified GABA neurons in monkey sensory motor cortex. *Journal of Neurocytology, 12*, 617–638.

Ip, N.Y., Ho, C. K., and Zigmond, R. E. (1982). Secretin and vasoactive intestinal polypeptide acutely increase tyrosine 3-monooxygenase in the rat superior cervical ganglion. *Proceedings of the National Academy of Sciences USA, 79*, 7566–7569.

Ip, N.Y., and Zigmond, R. E. (1984). Pattern of presynaptic nerve activity can determine the type of neurotransmitter regulating a postsynaptic event. *Nature, London, 311*, 472–474.

James, R., and Bradshaw, R. A. (1984). Polypeptide growth factors. *Annual Review of Biochemistry, 53*, 259–292.

Jan, L. Y., and Jan, Y. N. (1982). Peptidergic transmission in sympathetic ganglia of the frog. *Journal of Physiology, London, 327*, 219–246.

Jones, E. G. (1984). Identification and classification of intrinsic circuit elements in the neocortex. In G. M. Edelman, W. E. Gall, and W. M. Cowan (Eds.), *Dynamic aspects of neocortical function* (pp. 7–40). New York: John Wiley.

Jones, E.G., DeFelipe, J., Hendry, S.H.C., and Maggio, J.E. (1987). A study of tachykinin-immunoreactive neurons in monkey cerebral cortex. *Journal of Neuroscience*. (in press)

Jones, E.G., and Hendry, S.H.C. (1986). Co-localization of GABA and neuropeptides in neocortical neurons. *Trends in Neuroscience, 9*, 71–76.

Lin, C. -S., Lu, S. M., and Schmechel, D. M. (1985). Glutamic acid decarboxylase immunoreactivity in layer IV of barrel cortex of rat and mouse. *Journal of Neuroscience, 5*, 1934–1939.

Lundberg, A., Anggard, A., Fahrenkrug, J., Hökfelt, T., and Mutt, V. (1980). Vasoactive intestinal polypeptide in cholinergic neurons of exocrine glands: Functional significance of co-existing transmitters for vasodilation and secretion. *Proceedings of the National Academy of Sciences USA, 77*, 1651–1655.

McCulloch, J. (1983). Peptides and the microregulation of bloodflow in the brain. *Nature, London, 304*, 129.

McDonald, J. K., Parnavelas, J. G., Karamanlidis, A., and Brecha, N. (1982). The morphology and distribution of peptide-containing neurons in the adult and developing visual cortex of the rat. II. Vasoactive intestinal polypeptide. *Journal of Neurocytology, 11*, 825–837.

McDonald, J. F., Parnavelas, J. G., Karamanlidis, A., and Brecha, N. (1983). The morphology and distribution of peptide-containing neurons in the adult and developing visual cortex of the rat. IV. Avian pancreatic polypeptide. *Journal of Neurocytology, 11*, 985–995.

McDonald, J. K., Parnavelas, J. G., Karamanlidis, A., Brecha, N., and Koenig, J. I. (1982). The morphology and distribution of peptide-containing neurons in the adult and developing visual cortex of the rat. I. Somatostatin. *Journal of Neurocytology, 11*, 809–824.

McDonald, J. K., Parnavelas, J. G., Karamanlidis, A., Brecha, N., and Rosenquist, G. (1982). The morphology and distribution of peptide-containing neurons in the adult and developing visual cortex of the rat. III. Cholecystokinin. *Journal of Neurocytology, 11*, 881–895.

McGinty, J. F., van der Kooy, D., and Bloom, F. E. (1984). The distribution and morphology of opioid peptide immunoreactive neurons in the cerebral cortex of rats. *Journal of Neuroscience, 4*, 1104–1117.

Morrison, J. H., Benoit, R., Magistretti, P. J., and Bloom, F. E. (1983). Immunohistochemical distribution of pro-somatostatin-related peptides in cerebral cortex. *Brain Research, 262*, 344–351.

Muller, J. E., Straus, E., and Yalow, R. S. (1977). Cholecystokinin and its COOH-terminal octapeptide in the pig brain. *Proceedings of the National Academy of Sciences USA, 74*, 3035–3037.

Nestler, E. J., Walaas, S. I., and Greengard, P. (1984). Neuronal phosphoproteins: Physiological and clinical implications. *Science, 225*, 1357–1364.

Nilsson, J., von Euler, A. M., and Dalsgaard, C. -J. (1985). Stimulation of connective tissue cell growth by substance P and substance K. *Nature, London, 315*, 61–63.

Nishizuka, Y. (1984). Turnover of inositol phospholipids and signal transduction. *Science, 225*, 1365–1370.

Paxinos, G., Emson, P. C., and Cuello, A. C. (1978). The substance P projections to the frontal cortex and the substantia nigra. *Neuroscience*, *7*, 127–131.

Peters, A., Miller, M., and Kimerer, L. M. (1983). Cholecystokinin-like immunoreactive neurons in rat cerebral cortex. *Neuroscience*, *8*, 431–448.

Peters, A., Proskauer, C.C., and Ribak, C.E. (1982). Chandelier cells in rat visual cortex. *Journal of Comparative Neurology*, *206*, 397–416.

Ribak, C.E. (1978). Aspinous and sparsely-spinous stellate neurons contain glutamic acid decarboxylase in the visual cortex of rats. *Journal of Neurocytology*, *7*, 461–476.

Roach, A. H., Adler, J. E., Krause, J., and Black, I. B. (1985). Depolarization regulates the level of preprotachykinin messenger RNA in the cultured superior cervical ganglion. *Neuroscience Abstract*, *11*, 669.

Rockel, A. J., Hiorns, R. W., and Powell, T. P. S. (1980). The basic uniformity in structure of the neocortex. *Brain*, *103*, 221–244.

Rosser, M. N., Emson, P. C., Mountjoy, C. W., Roth, M., and Iversen, L. L. (1980). Reduced amounts of immunoreactive somatostatin in the temporal cortex in senile dementia of the Alzheimer type. *Neuroscience Letters*, *20*, 373–377.

Sachs, C., Hökfelt, T., Meyerson, B., Elde, R., and Rehfeld, J. (1977). Peptide neurons in human cerebral cortex–II. In W. A. den Hartog, G. W. Gruyn, and A. P. J. Heijstee (Eds.), *11th World Congress of Neurology*. Amsterdam: Excerpta Medica.

Said, S. I., and Rosenberg, R. N. (1976). Vasoactive intestinal polypeptide: Abundant immunoreactivity in neural cell lines and normal tissue. *Science*, *192*, 907–908.

Schmechel, D. E., Vickrey, B. G., Fitzpatrick, D., and Elde, R. P. (1984). GABAergic neurons of mammalian cerebral cortex: Widespread subclass defined by somatostatin content. *Neuroscience Letters*, *47*, 227–232.

Somogyi, P., Cowey, A., Halász, N., and Freund, T. F. (1981). Vertical organization of neurons accumulating [^{3}H]-GABA in visual cortex of rhesus monkey. *Nature, London*, *294*, 761–763.

Somogyi, P., Hodgson, A. J., Smith, A. D., Nunzi, M. G., Gorio, A., and Wu, J. -Y. (1984). Different populations of GABAergic neurons in the visual cortex and hippocampus of cat contain somatostatin–or cholecystokinin immunoreactive material. *Journal of Neuroscience*, *4*, 2590–2603.

Straus, E., Muller, J. E., Choi, H. S., Paronetto, F., and Yalow, R. S. (1977). Immunohistochemical localization in rabbit brain of a peptide resembling the COOH-terminal octapeptide of cholecystokinin. *Proceedings of the Academy of Sciences USA*, *74*, 3033–3034.

Streit, P. (1984). Glutamate and aspartate as transmitter candidates for systems of the cerebral cortex. In E. G. Jones and A. Peters (Eds.), *Cerebral cortex, Vol. 2, Functional properties of cortical cells* (pp. 119–143). New York: Plenum.

Uhl, G. R., and Snyder, S. H. (1976). Regional and subcellular distributions of brain neurotensin. *Life Science*, *19*, 1827–1832.