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Pathology of Parkinson's Disease

Changes Other than the Nigrostriatal Pathway

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ABSTRACT

In Parkinson's disease (PD), in addition to degeneration of the nigrostriatal dopaminergic pathway, a variety of neuronal systems are involved, causing multiple neuromediator dysfunctions that account for the complex patterns of functional deficits. Degeneration affects the dopaminergic mesocorticolimbic system, the noradrenergic locus ceruleus (oral parts) and motor vagal nucleus, the serotonergic raphe nuclei, the cholinergic nucleus basalis of Meynert, pedunculopontine nucleus pars compacta, Westphal-Edinger nucleus, and many peptidergic brainstem nuclei. Cell losses in subcortical projection nuclei range from 30 to 90% of controls; they are more severe in depressed and demented PD patients. Most of the lesions are region-specific, affecting not all neurons containing a specific transmitter or harboring Lewy bodies. In contrast to Alzheimer's disease (AD), subcortical system lesions in Parkinson's disease appear not to be related to cortical pathology, suggesting independent or concomitant degeneration. The pathogenesis of multiple-system changes contributing to chemical pathology and clinical course of Parkinson's disease are unknown.

Index Entries: Parkinson's disease; degeneration; neuropathology; subcortical systems; morphometry; neurochemistry.

INTRODUCTION

Degeneration of the dopaminergic nigrostriatal system associated with widespread Lewy bodies, the anatomical hallmarks of Parkinson's disease (PD), and the resulting striatal dopamine-deficiency syndrome are responsible for its classical motor symptoms (Hornykiewicz, 1975; Riederer et al., 1990). The substantia nigra zona compacta suffers a 60–85% loss of melaninized, tyrosine hydroxylase (TH) containing neurons, with more severe involvement of the mesostriatal neurons in the ventral tier of area 9, projecting to the putamen, than of the most medial (area A-10) and orodorsal portions projecting to the caudate nucleus (Hirsch et al. 1988; German et al., 1989,1990; Graybiel et al., 1990; Gibbs, 1990), and sparing of calbindin-binding neurons (Yamada et al., 1990). Nigral cell loss is more severe in the rigid-akinetic than in the tremor-dominant form (Paulus and Jellinger, 1991). Loss of mesostriatal neurons correlates significantly to the dorso-lateral-ventromedial gradient of TH-immunoreactive fiber loss in the striatum (Graybiel et al., 1990) and the decrease of striatal dopamine and its metabolites, which is more marked in the more dorsal than in the ventral parts of the striatum (Kish et al., 1988), corresponding to their reciprocal connection in the nigrostriatal loop (Alexander et al., 1986; Albin et al., 1989). However, the widespread occurrence of Lewy bodies (LB), being the principal cytoskeletal pathology of PD (Forno, 1986; Jellinger, 1989), and recent biochemical and neuropathologic data give evidence that the basic process is not limited to a single mediator-specific neuronal population (Agid et al., 1987,1990; Jellinger, 1989,1990 a,b; Halliday et al., 1990). PD appears to be a multisystem disorder involving a variety of subcortical neuronal systems and causing multiple neuromediator dysfunctions that result in complex patterns of functional and clinical deficits. Most of the lesions are not random, but region-specific, affecting not all neurons containing a specific transmitter or harboring LB. This review focuses on morphologic changes in different neuronal systems in PD in comparison to aging and with relevance to their pathogenesis, biochemical pathology, and clinical implications, including cognitive disorders.

MESOCORTICOLIMBIC DOPAMINERGIC SYSTEM

Lesions of the ventral tegmental area (VTA), the main source of the dopaminergic mesocorticolimbic system that projects to limbic forebrain, amygdala, neocortex, and upper brainstem (cf Swanson, 1982; Nieuwenhuys et al., 1988), have been reported in both PD and AD (Table 1). Loss of pigmented, TH-immunoreactive cells in the lower part of VTA (area A-10) and in the retrorubral region (A-8) ranges from 40 to 60%; in the central gray area, no gross cell loss has been observed (Uhl et al.,

Table 1
VTA (Area A-10): Neuronal Loss in PD and AD

Disorder	N	Age	Area	Neurol Loss in % controls	Author	Year
PD	5	72	A-10	40	Bogerts et al.	1983
	2		A-10	77	Javoy-Agid et al.	1984
	4	61	Ant.	64	Uhl et al.	1985
			Post.	45		
	15	82	A-10	45	Waters et al.	1988
	4	65	Melan.	49	Hirsch et al.	1988
			TH-IR	51		
	4	65	A-10	42–85	German et al.	1989
PEP	4	50	A-10	97	Bogerts et al.	1983
PSP	2	73	TH-IR	76	Hirsch et al.	1988
AD(DAT)		65–90	A-10	40–70	Mann et al.	1987
					Jellinger	1987

Ant. = anterior; Post. = posterior; Melan. = melanin-containing

1985; Hirsch et al., 1988). This is concordant with a 75% decrease in dopamine concentrations and 50–60% reduction in TH activity in the ventral mesencephalon (Javoy-Agid et al., 1981; Agid et al., 1987,1990), and the 40–60% decreases in dopamine levels in limbic and neocortical regions, especially in demented PD subjects (Ruberg and Agid, 1988). These show much lower densities of pigmented neurons in the medial substantia nigra (SN) (Fig. 1) that also projects to limbic and frontal areas (Rinne et al., 1989a; Paulus and Jellinger, 1991). Similar or less severe damage to the VTA occurs in AD (Mann et al., 1987; Gibb et al., 1989a). Behavioral disorders and dementia caused by damage to the nonstriatal dopaminergic mesocorticolimbic system have been observed (cf Torack and Morris, 1986, 1988; Verity et al., 1990).

NORADRENERGIC SYSTEM

The *locus ceruleus* (LC, area A-6), the main source of noradrenergic innervation, with the rostral mesencephalon, hypothalamus, motor vagal nucleus, hippocampus, and neocortex as major projection fields (cf Foote et al., 1983; Mann et al., 1983; Nieuwenhuys et al., 1988), has an internal regional topographic organization (Loughlin et al., 1986). Damage to the LC has been observed in normal aging, PD, AD, depression, and degenerative diseases (Table 2). Modern 3-D computer reconstruction methods and immunohistochemistry show a 24–54% global cell loss in aged humans, with predominant damage to the rostral parts projecting to neocortex and hippocampus, and no or very little lesions in caudal parts of LC projecting to the cerebellum and spinal cord (Ingram et al., 1987; Zweig et al., 1988b; Chan-Paley and Asan, 1989b). In PD, LC neuro-

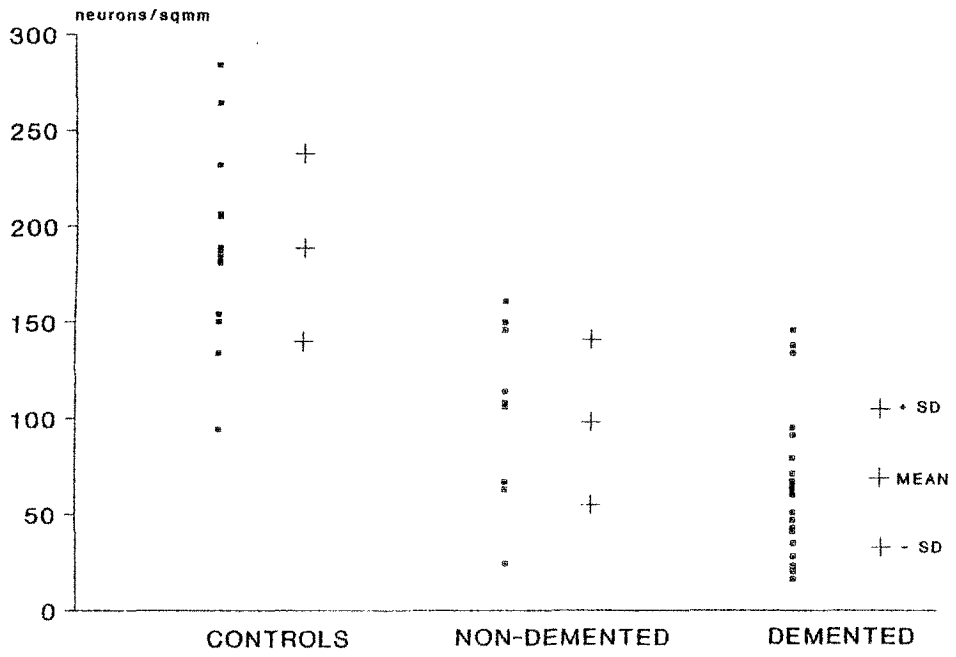

Fig. 1. Neuronal density in medial substantia nigra zona compacta in controls (n = 14; mean age, 76.4 yr), and nondemented (n = 10) and demented PD subjects (n = 20), both with a mean age of 77 yr.

nal loss ranges from 28 to 94%, with an average of 64% (German et al., 1990) and 70–80% loss of melanin, whereas the capacity for protein synthesis in the remaining neurons, expressed by their nucleolar volume, seems to be maintained in normal aging and even in later stages of PD (*see* Mann et al., 1983; Mann and Yates, 1983). LC neuronal loss is more severe in the rigid-akinetic type (mean 75%) than in the tremor-dominant type, with a mean of 44% (Fig. 2). In general, LC damage is less severe in nondemented PD subjects (28–31%) than in demented ones (48–88%), in whom it approaches the values seen in AD with a range of 25–90% (Table 2). Almost 95% cell loss was observed in demented PD patients not responding to L-dopa treatment (Chan-Palay and Asan, 1989a). Similar cell depletion of LC is seen in olivopontocerebellar atrophy (OPCA); in progressive supranuclear palsy (PSP), it averages 50% (Table 2). In PD, damage to the LC is associated with LBs in over 99% and neurofibrillary tangles (NFT) in 17% of the cases. In AD, LBs are present in 66% and NFTs in 85% (Jellinger, 1989), with the highest density in the severely involved midportion of LC (Zweig et al., 1988b,1989b). NFTs affect most of the LC neurons in PSP and boxer's dementia (Mann et al., 1983; Agid et al., 1990). LC shows neurons immunoreactive for tau in young nondemented subjects, prior to the hippocampus (Shin et al., 1991). Topographic arrangement of LC lesions differs in various diseases:

Whereas in normal aging, AD or DAT (Alzheimer's-type dementia), and PD with dementia, cell loss is highest in the oral and middle parts, with comparative preservation of the caudal portions (Marcyniuk et al., 1986,1989; Bondareff et al., 1987; Ingram et al., 1987; German et al., 1988b,1990; Zweig et al., 1988a,1989; Chan-Palay and Asan, 1989a), PD shows either diffuse cell reduction in all regions of LC, mainly in the central third (German et al., 1990), or more severe involvement of the middle and caudal portions than the rostral ones (Chan-Palay and Asan, 1989b). Assuming a topographic arrangement of LC neurons, the greater loss in rostral portions projecting to temporal cortex and hippocampus and significant correlations to the density of plaques and NFTs in AD cortex (Tomlinson et al., 1981; Marcyniuk et al., 1986) suggest a retrograde degeneration of LC attributable to primary damage to its cortical target areas (German et al., 1987; Chan-Palay and Asan, 1989b). Another hypothesis suggests that degeneration of adrenergic neurons in LC, attributable to anterograde degeneration and metabolic interaction, causes neuronal death in cortical areas in AD (Hertz, 1989). Although AD shows negative correlation between LC cell loss and age (Zweig et al., 1988b), no such relationship between LC cell loss with cortical AD pathology or age is known in PD, suggesting independent or parallel degeneration of this nucleus (Jellinger, 1990a). LC damage results in severe loss in cortical and limbic noradrenergic innervation, with 40–75% decrease of norepinephrine (NE), its metabolites, and related enzymes in neocortex and hippocampus in both AD (Arai et al., 1984a; Palmer et al., 1987; Sofic et al., 1988; Reinikainen et al., 1988b) and PD (Birkmayer and Riederer, 1985). This is mainly seen in demented PD patients (Cash et al., 1987; Ruberg and Agid, 1988) with severe neuronal loss in LC (Gaspar and Gray, 1984; Heilig et al., 1985; Chui et al., 1986; Zweig et al., 1988b,1989b; Chan-Palay and Asan, 1989b; Mizutani et al., 1990), which is associated with reduction of NE and its metabolites in LC (Cash et al., 1987). Severe LC damage is also seen in depression (Chan-Palay and Asan, 1989a), particularly in demented AD subjects with depression who have significantly fewer neurons in mid-LC (Zweig et al., 1989b) and a ten- to 20-fold decrease in cortical NE levels (Zubenko et al., 1990).

In PD, the more severe involvement of the middle and caudal LC produces reduced NE innervation of the cerebellum and spinal cord, where loss of TH-immunoreactive neurons and fibers in laminae I and X (Jellinger, 1989) and decrease in dopamine and NE are seen (Scatton et al., 1987). In both PD and AD, not only are adrenergic TH-immunoreactive (TH-IR) cells involved, but also there is major loss of neuropeptide-immunoreactive neurons in the oral and middle parts of LC in PD subjects with and without dementia, and, in AD, the caudal parts of the LC are preserved (Chan-Palay and Asan, 1989b).

In PD the melanin-pigmented neurons of the arcuate and periventricular hypothalamic nuclei are preserved (Matzuk and Sapar, 1985), but

Table 2
Locus ceruleus: Neuronal Losses in PD, Aging and AD

Disorder	N	Age	Area	Neuron Loss (% of Controls)	Author	Year
PD	6	66	total	78.5	Mann et al.	1984
PD untreated	4	63	total	72.2	Mann et al.	1984
treated	4	73	total	85.3		
PD, no dementia	11	?	oral	53	Zweig et al.	1988b
			mid	63		
			caudal	68		
PD, no dementia	2	80	total	31	Chan-Palay and Asan	1989
PD + dementia	3	86	total	48.3		
PD+D/Dopa-neg.	2	81	total	94.4		
PD ± dementia	4	75	TH-IR	45	Halliday et al.	1990
PD ± dementia	37	77	total	63.5	Jellinger and Paulus	1990
− RA-type	21	77	total	74		
T-type	16	77	total	52		
PD, no dementia	2	75	total	28	Mizutani et al.	1991
PSP	4	66	total	88	Mann et al.	1984
OPCA	2	?	total	85–90	Tomonaga	1983

Normal aging		15/104	total	24–70	Vijayshankar and Brody	1979
					Mann et al.	1984
					German et al.	1988a,b
					Chan-Palay and Asan	1989
AD (<70 y)	1	67	total	79	Tomonaga	1983
	7	67.2	total	68.5	Ichimija et al.	1986
	1	66.0	total	68.0	Ingram et al.	1987
			centr.	72.0		
			ventr.	15.0		
	28	72.0	oral	70.0	Zweig et al.	1988b
			mid	81.0		
			caud.	67.0		
DAT (>70 y)	24	74–87	total	40.0	Vijayshankar and Brody	1979
	15	81	total	51–56	Tomlinson	1989
	20	78 + 7	total	80.0	Bondareff et al.	1982
	22	74.5	total	70.3	Mann et al.	1984
	5	75.6	total	41.2 (30–86)	Chui et al.	1986
	9	75.8	total	33.0	Burke et al.	1988
	3	76	total	3.5–87.5	Chan-Palay and Asan	1989
	18	82.4	total	50.3	Jellinger	1990a

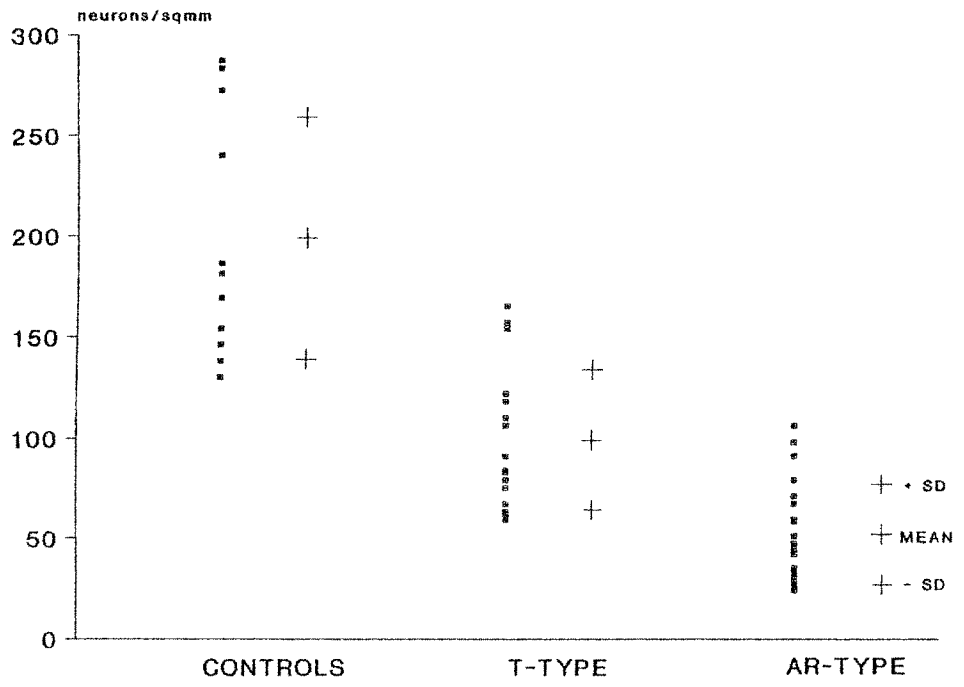

Fig. 2. Neuronal density in locus ceruleus in PD subjects with AR (rigidity-akinesia) type (n = 28) and T (tremor-dominant) type (n = 15) vs age-matched controls.

a 25–35% decrease in nucleolar volume and cytoplasmic RNS and a loss of TH-IR cells in the related hypothalamic paraventricular and supraoptic nuclei (Jellinger, 1989) indicate reduction in NE hypothalamic input. The decline in functional capacity of hypothalamic neurons as a result of degeneration of the ascending NE pathways based on the LC is more severe in demented PD cases (Mann and Yates, 1983). In AD, loss of large neurons in the supraoptic and paraventricular nuclei correlates to LC cell depletion, but not to age (Mann et al., 1985b). Recent studies, however, in aging and AD, revealed no cell loss in the supraoptic and paraventricular nuclei as a result of activation of vasopressin (Goudsmit et al., 1990). Neuronal hypertrophy may represent a compensatory mechanism for age-related decline in NE innervation of the hypothalamus (Vogels et al., 1990b), which, in AD, shows no changes in NE levels (Sparkes et al., 1988). Central NE deficiency caused by degeneration of the ascending LC system has been related to mental changes and depression in PD and AD (Agid et al., 1987; Zweig et al., 1988b; Zubenko et al., 1990).

The noradrenergic *dorsal vagal nucleus* has been reported to show no or only very little changes in aged controls, PD, and PSP (Mann et al.,

1983), with 5–17% cell loss, but frequent occurrence of LB, whereas in AD, cell depletion ranges from 30 to 44% (Table 3). Recently, Halliday et al. (1990a) reported a 77% loss in substance P (SP) immunoreactive preganglionic cells of the dorsal motor vagus nucleus, whereas the noradrenergic TH-IR neurons, although often harboring LB, are not severely affected (<5% reduction). These data confirm earlier findings of degeneration of the motor preganglionic neurons with relative sparing of the pigmented ones (Eadie, 1963), although the presence of many LBs in noncatecholaminergic neurons may indicate that the degeneration of the motor vagal nucleus is caused by a primary process and is not secondary to damage to pathways that synapse with these neurons (Halliday et al., 1990a). Loss of SP-IR vagal neurons, involvement by LBs of peripheral autonomic neurons is enteric plexuses (Wakabayashi et al., 1988), and reduced TH-immunoreactivity in adrenal medulla (Riederer et al., 1978), with significant decrease of dopamine (Carmichael et al., 1988), indicate damage to the sympathetic noradrenergic system that may contribute to vegetative symptoms in PD (Birkmayer and Riederer, 1985; Korczyn, 1989; Halliday et al., 1990b; Agid et al., 1990).

Recent morphometric studies of the adrenergic nuclei A-1 and A-2 in the medulla oblongata containing poorly pigmented neurons revealed no cell loss in PD or PSP, but considerable degeneration of these nuclei in striatonigral degeneration (Malessa et al., 1990).

SEROTONERGIC SYSTEM

The *dorsal raphe nucleus* (DRN) or nucleus supratrochlearis (Olszewski and Baxter, 1982) and the central superior (raphe) nucleus, corresponding to cell groups B6–8 (Nieuwenhuys et al., 1988), the large neurons of which are serotonin-immunoreactive (Zweig et al., 1988), give rise to the ascending serotonergic pathways and are bidirectionally connected with many central nervous system (CNS) centers (cf Steinbusch, 1984; Nieuwenhuys et al., 1988). Damage to these nuclei has been reported in both PD and AD (Table 4). Loss of large DRN cells ranges in PD from 0 to 42%, and in AD from 6 to 76% with mean values between 20 and 40%. Rostrocaudal increase of cell loss reflects topographic projection patterns of the nucleus (Zweig et al., 1988a). Cell loss at all levels of DRN is significantly greater in depressed than in nondepressed PD (Fig. 3) and AD subjects who show significantly fewer neurons at the rostral level of the median raphe nucleus (NCS) (Zweig et al., 1988a). Although it projects to the hippocampus and other regions severely affected in AD (Imai et al., 1986), no cell losses, but many cells involved by NFT, are seen in AD (Zweig et al., 1988). In PD, the DRN (A-10) shows a severe decrease of TH-IR cells, whereas phenylalanine hydroxylase (Ph-8)-IR

Table 3
Quantitative Changes in Some Noradrenergic Nuclei in PD and AD

Nucleus	Neurons	Volume content (% loss of control) Nucleolar	RNA	Disorder	Age	Author	Year
Supraoptic	0	27.4	23.6	PD	68	Mann et al.	1983
Nucleus	65			DAT	85	Mann et al.	1985b
	0			AD		Goudsmit et al.	1990
Paraventricular							
Nucl.	0	31.2	28.7	PD	68	Mann et al.	1983
		48.1		DAT	85	Mann et al.	1985b
	0			AD		Goudsmit et al.	1990
Dorsal	0	16.6	12.8	PD	68	Mann et al.	1983
Motor	5	(TH-IR)		PD	75	Halliday et al.	1990b
	77	(SP-IR)					
	30	36.2		DAT	85	Mann et al.	1984
	44	43		AD	66		
	30			Aging	15/92		
A1/A2	0			PD		Malessa et al.	1990
(oblongata)							

Table 4
Dorsal Raphe Nucleus: Neuronal Loss in PD, Aging and DAT

Disease	N	Age	Neuronal loss (% controls)	Author	Year
PD	8	68	0	Mann and Yates	1983
	28	78	42.4 (29–43)	Jellinger	1989
	4	75	24 (DR)	Halliday et al.	1990b
			60 (MR)	(PH-8 immunostain)	
			44 (RO)		
	23	77	37.2	Paulus and Jellinger	1991
AR-type	13	77	44		
T-type	10	77	32		
PD, depr.	14	77	51		
non-depr.	9	77	44		
Guam-PDC	4		50–90	Yamamoto and Hirano	1985
Normal	15/92		7	Mann et al.	1983
Aging					
AD (<70 y)	12	66	17.4 ± 6	Mann et al.	1984
	4	63	36.6 (23–48)	Tabaton et al.	1985
	7	67	21.0	Ichimiya et al.	1986
	9	67.2	33.7 ± 9	Jellinger	1989
DAT (>70 y)	19	84.7	6.1 ± 1.6	Mann et al.	1984
	7	87.7	16.6 ± 4 (tot)	Curcio and Kemper	1984
			27.3 ± 5 (large)		
	5	74.2	76.9 ± 15	Yamamoto and Hirano	1985
	25	72.5	10 (oral)	Zweig et al.	1988b
			15 (mid)		
			36 (caud.)		
	14	81.9	42.7 ± 7 (large)	Jellinger	1989

DR = dorsal raphe; MR = medial raphe; RO = raphe obscurus

serotonergic neurons are unaffected (Halliday et al., 1990b). By contrast, there is about 60% reduction of PH-8$^+$ serotonin-synthesizing neurons in the NCS of caudal midbrain and pons (Halliday et al., 1990a,b). In PD, 5–6% of the remaining DRN neurons and many of the PH-8$^+$ cells contain LB, and a few of them show NFT, whereas in AD, and especially in those with Guam Parkinson-dementia complex (PDC), suffering a DRN cell loss of 50–60%, most of the cells harbor NFT (Yamamoto and Hirano, 1985). In AD, the DRN and NCS have the highest incidence of NFT in the brainstem, showing many times as many NFTs as nondemented aged subjects (Tomlinson, 1989).

Considerable functional damage to the central serotonergic system was confirmed by biochemical studies that show a large reduction of serotonin (5-HT) and its metabolites in many brain regions in both PD and AD (Ichimiya et al., 1986; Mann and Yates, 1986; D'Amato et al., 1987; Agid et al., 1987,1990) and reduced densities of striatal and cortical

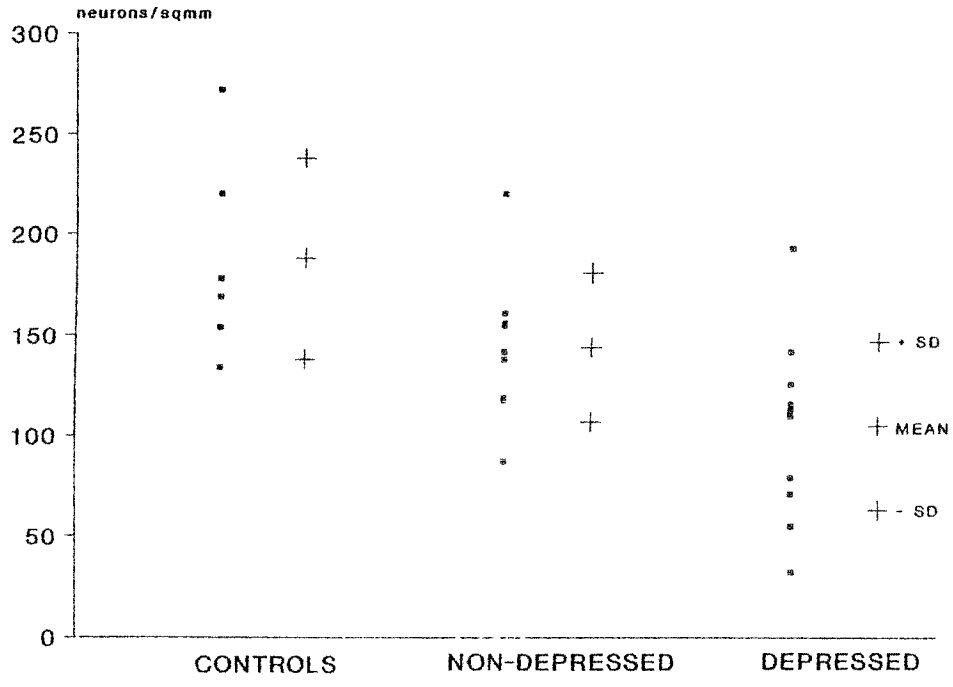

Fig. 3. Neuronal density in dorsal raphe nucleus in PD subjects with (n = 9) and without depression (n = 8) vs controls (n = 8).

5-HT S1 and S2 binding sites in these disorders (Cross et al., 1984; Quirion et al., 1986; Maloteaux et al., 1988). Reduction of serotonin in the forebrain is presumably caused by severe loss of serotonergic neurons in both the DRN and median raphe nucleus of the midbrain and pons; loss of serotonergic cells in the medullary raphe may correspond to loss of serotonergic markers in the spinal cord (Scatton et al., 1986). In PD, the distinct anatomical and functional populations of serotonergic neurons in the median and dorsal raphe nuclei (Mulligan and Tork, 1988) appear to be affected in different ways: only the fast-acting, target-specific serotonergic system of the median raphe is affected; the slower and more widely distributed system of the DRN remains intact (Halliday et al., 1990a), although it is considerably damaged in depressed AD and PD subjects. Alterations in serotonin metabolism have been related to depression in PD and AD (Crow et al., 1984; Mayeux, 1990). Decreased levels of serotonin and its metabolites are seen in a variety of depression disorders (cf Meltzer, 1989), but studies in postmortem brains from subjects with PD and major depression showed different ratios of biogenic amines (Birkmayer and Riederer, 1986). Hence, the functional importance of degeneration of the ascending serotonergic system awaits further elucidation.

CHOLINERGIC SYSTEMS

Nucleus Basalis of Meynert (NBM)

The NBM in the substantia innominata of the basal forebrain was one of the nuclei in which LBs were first observed in PD by Lewy (1913). Hassler (1938) noted that cell loss in NBM did not correlate to the severity of the extrapyramidal syndrome and suggested that it may represent the anatomical substrate of bradyphrenia. Based on the distribution of choline acetyltransferase (ChAT) positive neurons, the NBM can be subdivided into four regions (Mesulam and Geula, 1988): the medial septal nucleus (Ch1 region), the ventral and horizontal nuclei of the diagonal band of Broca (Ch2 and Ch3 regions), and the NBM (Ch4 region) that is separated into the anterior (Ch4a), intermediate (Ch4i), and posterior (Ch4p) parts. The large NBM neurons that react with ChAT and acetylcholinesterase (AChE) provide the major cholinergic input to the isocortex, hippocampus, and midbrain, and the NBM receives projections from limbic, paralimbic, and subcortical areas (Hedreen et al., 1984; Ezrin-Waters and Resch, 1986; Steriade and Biesold, 1990).

In normal aging, there is no or only insignificant neuronal loss in the anterior parts of the basal forebrain projecting to hippocampus, with no age-dependent variations in cortical ChAT activity (Davies, 1988; Vogels et al., 1990b) or density of cholinergic fibers (Geula and Mesulam, 1989). However, a number of investigators have reported decreases with age in cortical ChAT activity in subjects with preserved mental status (Davies et al., 1980; McGeer et al., 1984; Katzman et al., 1988). In AD, severe neuronal loss with frequent plaques and/or NFT are seen in NBM, ranging from 15 to 90%, with an average overall cell loss of 15–30% and significant depletion (36–70%) of large cholinergic neurons in the intermediate and posterior parts of the Ch4 region (Table 5). Morphologic and biochemical lesions are symmetrical (Moossy et al., 1988; Zubenko et al., 1988), and no differences in cell numbers are seen between early- and late-onset AD (Vogels et al., 1990b). In AD, magnocellular NBM cell loss has significant correlations to neuronal loss, density or plaques and NFT, and activity of presynaptic cholinergic marker enzymes and nicotinic/M_2 receptors in the temporal target areas (Arendt et al., 1985; Etienne et al., 1986; Perry et al., 1987,1989; Reinikainen et al., 1988a) suggesting retrograde or anterograde degeneration of the NBM neurons (Pearson and Powell, 1987; Allen et al., 1988). Apart from cell loss, shrinkage of large neurons is a characteristic feature of degeneration of the cholinergic NBM system, suggesting reduced enzyme synthesis or failure of transport as a result of neurotrophic factor dysfunctions (Allen et al., 1988; Vogels et al., 1990b). This is accompanied by severe decrease of cholinergic innervation of cortex and hippocampus (Allen et al., 1988; Ransmayer et al., 1989), whereas decrease in muscarinic cholinergic receptors in the hippocampus of AD brains may result from neuronal loss (Probst et al., 1989).

Table 5
Neuronal Loss in Nucleus Basalis of Meynert in Aging and AD

Condition	Region	Neuron loss %	reducion density max %	reducion density mean	Author	Year
Normal Aging	Ch 4		0		Chui et al.	1983
(0–90 y)	Ch 4	70.0			McGeer et al.	1984
	Ch 4a			35.0	Mann et al.	1984
	Ch 4	23.0			Loew-Hummel et al.	1987a
	Ch 1–4	0			Bigl et al.	1987
	Ch 1–4	0	0		Vogels et al.	1990
AD/DAT	Ch 4	.75–90			Whitehouse	1982
		55			Candy et al.	1983
			ChAT	18.0	Pearson et al.	1985
			AChE	14.0		
		70	54.0		Arendt et al.	1983
		39–62			Wilcock and Esiri	1982
	Ch 1,2	46			Gertz et al.	1987
	Ch 2			39–70	Etienne et al.	1986
	Ch 4i			41–87	Doucette et al.	1986
	Ch 4	64		25–29	Rinne et al.	1987
	Ch 4p			57–80	Wilcock et al.	1988
	Ch 4	61.0	(large)		Allen et al.	1988
	Ch 4	55–70	54–73	22–76	Jellinger (Lit)	1989
	Ch 1,2	0			Vogels et al.	1990a
	tot.	15.5				
	Ch 4	19.5	(58% large)			
	Ch 4p	36.0	(70% large)			

In PD, the NBM cell depletion ranges from 0 to 77%, with means of 30–40% and more severe involvement of the intermediate and posterior parts of Ch4 projecting to the neocortex (Table 6). The extent of NBM cell loss shows no correlation to age or duration of illness (Tagliavini et al., 1984). Irrespective of cortical pathology, NBM neuronal depletion is much higher in demented PD patients (50–77%), in whom it approaches the values in AD, than in nondemented subjects (range 0–40%), who show values only slightly higher than those in aged controls (Tables 5 and 6). Cell loss involves mainly the magnocellular Ch4i and Ch4p areas, with comparative preservation of the Ch2 and Ch3 portions, where significant neuronal loss may occur in AD (Etienne et al., 1986). There are reduced numbers of cells in NBM (Ch4) reacting with nerve growth factor receptors, colocalized with cholinergic neurons (Mufson et al., 1990). The nucleolar volumes of the remaining NBM neurons in PD remain unchanged (Tagliavini et al., 1984) or show considerable decrease in protein synthetic capacity, with a reduction in nucleolar volume or RNA content of 20–22%, compared with a 30–35% decrease in AD (Mann et al., 1983). LBs in the NBM are seen in 85–98%, and NFT in 30–65%, of all PD brains; their prevalence in AD is about 100%, with LBs in 10–15% (Jellinger, 1989). In contrast to AD, neuritic plaques are rare in nondemented PD subjects (Gaspar and Gray, 1984; Nakano and Hirano, 1984).

Severe depletion of the NBM with 75–80% loss of large cholinergic neurons is seen in Diffuse Lewy Body Disease (DLBD), usually associated with dementia, cortical amyloid deposits but absence of neuritic plaques, and sparing of the hippocampus, thus differing from true AD (Dickson et al., 1989; Perry et al., 1990). In Guam PDC loss of large NBM cells ranges from 60 to 93%, without decrease in cortical ChAT activity. In PSP, NBM cell loss averages 40%, but, in contrast to AD, its extent shows negative correlation to age (Tagliavini et al., 1984). In a case of boxer's dementia with parkinsonism, Uhl et al. (1982) reported a 40% depletion of NBM cells with reduced cortical ChAT activity. In all these conditions associated with dementia, most or all subdivisions of the NBM are involved (Dickson et al., 1989; Agid et al., 1990), whereas postencephalitic parkinsonism (PEP) reveals no or only little damage to the NBM (Table 6) except for the frequent occurrence of NFTs (Candy et al., 1983; Arendt et al., 1988; Jellinger, 1989).

Neuronal loss in the NBM in PD, DLDB, and PSP is associated with reduced cortical and NBM levels of presynaptic cholinergic marker enzymes ChAT and AChE (Perry et al., 1983,1985; Gaspar and Gray, 1984; Ruberg et al., 1985; Dickson et al., 1989; Agid et al., 1987, 1990) and a 30–55% decrease of cortical nicotinic receptors (Whitehouse et al., 1988), particularly in temporal cortex of demented PD subjects (Sirvio et al., 1989), whereas the predominantly postsynaptic low-affinity muscarinic receptor binding is increased in PD and DLDB, possibly as a result of the absence of NFT formation. The suggested denervation-induced muscarinic supersensitivity in cholinoreceptive cortical cells is supported by

Table 6
Neuronal Loss in Nucleus Basalis of Meynert in PD

Disorder	Area	N	Neuron loss %	Density reduction max. %	Density reduction mean	Author	Year
PD	Ch 1,4	14	77.0	70.0		Arendt et al.	1983
	Ch 4	32	47.0	46.0		Gaspar and Gray	1984
	Ch 4	11	60.0		52.9	Nakano and Hirano	1984
	Ch 4	6	45.8			Tagliavini and Pilleri	1984
	Ch 4	50	58.0			Jellinger	1986
	total	1	0			Vogels et al.	1990b
PD[nd]	Ch 4	4	33.3	± 6.2		Whitehouse et al.	1983
		14	32.0	33.2		Gaspar and Gray	1984
		1	40.0			Rogers et al.	1985
		2	0			Mizutani et al.	1990
PD[d]	Ch 4	3	77.1	53.1		Whitehouse et al.	1983
		18	60.0	58.0		Gaspar and Gray	1984
		3	51.7			Tagliavini and Pilleri	1984
		3	75.0			Rogers et al.	1985
		33	69.5	64.2	66.6	Jellinger	1986
		3	57.0			Mizutani et al.	1990
PD-C	Ch 4	2	93.0		85.0	Nakano and Hirano	1985
		3	60.0	(large)	43.1	Masullo et al.	1988
PSP	Ch 4	6	44.0			Tagliavini and Pilleri	1984
		2	40.0			Rogers et al.	1985
PEP	Ch 4	7	0	26.0		Arendt et al.	1983
		7	0			Candy et al.	1983
		1	15.7	0		Whitehouse et al.	1983

[nd]nondemented [d]demented

the quantitative relationship in temporal cortex of PD and DLDB between receptor binding and ChAT, whereas this supersensitivity is not evident in AD (Rinne et al., 1989b; Perry et al., 1990). Cortical nicotinic receptors, however, are also reduced in PD cases without dementia (Perry et al., 1987), and no relations have been found among the severity of NBM cell loss, cortical ChAT deficiency, and the degree of cortical AD lesions (Gaspar and Gray, 1984; Perry et al., 1985; Chui et al., 1986; Jellinger, 1989). These data, the unevenness of cell loss in different parts of the NBM, and the variable correlations of NBM and ChAT reduction in both neocortex and hippocampus suggest independent or concomitant rather than secondary transneuronal degeneration of the cortical and subcortical systems in PD, a process that has also been proposed for AD (Saper et al., 1985; Etienne et al., 1986). The demonstration of dendritic, possibly regenerative NBM changes in AD (Arendt et al., 1986) and of altered lipofuscin pigmentation in PD (Ulfig, 1989) have been interpreted as signs of neuronal plasticity in these disorders.

Cholinergic deficiency caused by degeneration of the ascending innominatocortical system is believed to play a role in cognitive disorders in AD and PD (Perry, 1986; Agid et al., 1990). Although some authors found no correlation between cell loss in NBM and mental status in PD subjects (Tagliavini et al., 1984), both NBM cell loss and cholinergic deficits in cortex and NBM are usually greater in demented PD subjects (Gaspar and Gray, 1984; Perry et al., 1983,1985; Dubois et al., 1985). Comparative autopsy studies in 50 PD patients showed that in the nondemented ones, NBM cell loss ranging from 15 to 62% was associated with little or no cortical AD pathology; in demented cases, NBM cell depletion ranged from 64 to 90% and was often, but inconsistently, accompanied by severe cortical AD lesions (Jellinger, 1989). The demonstration of frontal cholinergic deficiency (Perry et al., 1985; Dubois et al., 1985; Sirvio et al., 1989) and of neuronal loss in the NBM (Nakano and Hirano, 1984; Jellinger, 1989,1990b) in PD patients without cognitive impairment indicate that the ascending cholinergic system is already in the process of degeneration and that there may be a critical threshhold level for the cholinergic deficit before dementia becomes apparent. It can be concluded that this threshold level—similar to that in the nigrostriatal dopaminergic system producing motor PD signs at about 80% loss of striatal dopamine (Bernheimer et al., 1973)—lies at about 65–80% neuronal loss and/or shrinkage within the NBM with equivalent cortical cholinergic denervation that cannot be compensated for by various mechanisms, such as increases the density of muscarinic receptors (Dubois et al., 1985; Probst et al., 1989; Perry et al., 1990) or vesicular storage of AChE (Dubois et al., 1990). By analogy with AD, degeneration of the ascending innominatocortical system and the resulting cholinergic deficiency may contribute to cognitive changes and subcorticofrontal behavioral impairment in PD (Dubois et al., 1990), but the unevenness of cholinergic deprivation in the different subdivisions of the NBM and its

variable correlation to cholinergic deficits in both the NBM and neocortex emphasize that the basic mechanisms for the dysfunction of the cholinergic forebrain in PD and its relation to cognitive impairment await further studies.

Pedunculopontine Tegmental Nucleus

The nucleus tegmenti pedunculopontinus, pars compacta (PPNc) is a cholinergic nucleus in the dorsolateral part of the caudal mesencephalic tegmentum, the cells of which react with ChAT, AChE, SP, and NADPH diaphorase, and probably belong to the cholinergic cell group Ch5 (Mesulam and Mufson, 1984; Mufson et al., 1988; Halliday et al., 1990a). It is recognized as an important loop nucleus, receiving fibers and providing major projections to the thalamus, substantia nigra zona compacta, subthalamic nucleus, striopallidum, pontine tegmentum, basal forebrain, and minor projections to widespread cortical areas (Scarnati et al., 1987; Hallinger et al., 1987). The PPNc is considered an extrapyramidal center for affecting the balance between cholinergic and dopaminergic functions of the basal ganglia (cf Graybiel, 1989; Steriade and Biesold, 1990).

Severe cell loss in the PPNc (75–80%) has been observed in PSP (Table 7) (Hirsch et al., 1987; Zweig et al., 1988a) and in patients with PD, in whom it ranges from 36 to 57%, with loss of 57% of the SP-immunoreactive cells (Table 8), and strong correlation to neuron loss in the SN zona compacta, but negative correlations to the patients' age, the duration of illness, and Lewy body counts (Zweig et al., 1989b). Less severe neuronal depletion of the PPNc is observed in AD (range 25–34%), where 25–38% of the neurons contain NFTs (Mufson et al., 1987; Jellinger, 1988; Zweig et al., 1989b). These data suggest a more severe involvement of the putative cholinergic and SP^+ PPNc neurons in PSP and PD than in AD. Overactivity of the NPPc in experimental MPTP parkinsonism in cynomolgus monkeys (Mitchell et al., 1990) could indicate dysfunctions in the tegmentonigrosubthalamocortical pathways, although the clinical significance of the nucleus in PD remains unclear. Recent findings that the parameters of cholinergic transmission in the thalamus and subthalamic nucleus remain unaltered in PD and AD suggest that the involvement of the PPNc is a secondary retrograde phenomenon rather than part of a systemic cholinergic fiber degeneration (Xuereb et al., 1990). Damage to the PPNc may contribute to disorders of locomotor activities, abnormalities of gait and posture (Coles et al., 1989), coordination of the sleeping–waking cycle (disturbances of parodoxial sleep), or cognitive disturbances in PD and related disorders (Zweig et al., 1989b).

Westphal-Edinger Nucleus

The Westphal-Edinger nucleus, a visceral subdivision of the oculomotor complex, giving rise to cholinergic fibers to the ciliary ganglion regulating pupilloconstriction (Bender, 1980), suffers a 54% neuronal loss

Table 7
The Pedunculopontine Nucleus in PD, PSP, and AD

Disorder	N	Age	Neuron Loss (% controls)	Author	Year
PD	6	73 ± 11	57	Hirsch et al.	1987
	11	76.6	49 (43–51)	Jellinger	1988
	4	77	46	Zweig et al.	1989a
	4	75	57	Halliday et al.	1990b
PSP	3	73 ± 10	79	Hirsch et al.	1987
	2	62.7	75	Jellinger	1988
AD/DAT	5	59.4	33.8	Jellinger	1988
	11	85.4	25.7		

Table 8
Reduction of Immunoreactive Brainstem Neurons in PD
(Halliday et al., 1990a,b)

Marker	Region	% Reduction	Significance
TH	Midbrain (Area 8,9,10)	68	s
	Pons (*L. ceruleus*)	55	s
	Medulla (area 1 and 2)	20	ns
PNMT	Medulla oblongata	41	s
PH-8	Dorsal raphe	24	ns
	Median raphe	60	s
	Raphe obscurus	44	s
SP	Pedunculopontine nucleus	57	s
	Raphe obscurus	58	s
	Lateral medulla	85	s
	Dorsal motor vagal nucl.	77	s
NP-Y	Medulla oblongata	70	s

s: significant (Student's *t*-test) ns: not significant

in PD, and 2–3% of the cells are affected by LBs or NFTs (Hunter, 1985). Among 50 PD brains, LBs and NFTs were observed in 94 and 29%, respectively; in 50 AD cases, their prevalence was 13 and 89%, respectively (Jellinger, 1990c). In PSP, these and other cholinergic mesencephalic nuclei suffer a significant decrease in the number of neurons with ChAT-IR (69 to 93%), indicating a regionally selective destruction of cholinergic neurons (Juncos et al., 1991). Damage of this nucleus may explain neuroophthalmic dysfunctions in PD, AD and/or PSP (Guiloff et al., 1980; White et al., 1983; Rascol et al., 1989; Juncos et al., 1991).

PEPTIDERGIC SYSTEMS

Neuropeptides are thought to modulate the excitability of dopaminergic neurons in the extrapyramidal system (cf Graybiel, 1986; McGeer and McGeer, 1989). Whereas some neuropeptides are severely decreased,

by 15–75%, in several regions of the brain in both PD (cf Constantinidis et al., 1988; Agid et al., 1990) and AD (cf Nemeroff et al., 1989; Ferrier and Leake, 1990), other substances show no selective changes, although the literature is quite controversial with respect to many neuropeptides (cf Constantinidis et al., 1988; Whitford et al., 1988; Beal et al., 1988; Waters et al.,1988; Kowall and Beal, 1988; Gaspar et al., 1989; Nemeroff et al., 1989; Bowen, 1990; Agid et al., 1990; Ferrier and Leake, 1990; Halliday et al., 1990a). Here, only changes of major neuropeptides are considered.

Cholecystokinin (CCK-8)

Immunoreactivity of CCK-8, a component of some ascending dopaminergic systems (Hökfelt et al., 1987; Dietl et al., 1987), in PD brain shows a 36–40% reduction in SN, probably resulting from degeneration of nondopaminergic CCK-8 neurons without considerable changes in other CNS regions, such as the cerebral cortex, striatum, VTA, and hypothalamus (Studler and Javoy-Agid, 1985). CCK-8 has an excitatory effect on dopamine neurons in the SN and modulates the activity of nigrostriatal cells; CCK deficiency may affect the expression of motor symptoms in PD (Agid et al., 1987). In AD, cortical CCK-8 is unchanged or mildly reduced (Perry et al., 1981; Rossor et al., 1984; Constantinidis et al., 1988).

Met-Enkephalin (M-Enk)

M-Enk that appears closely related to the dopaminergic systems (Graybiel, 1986) is suggested to regulate some activities of nigrostriatal neurons. Radioimmunoassay of PD brain showed a 70% loss of M-Enk in SN compacta and in VTA, and 50% loss in putamen and pallidum, but no changes in caudatum, accumbens, or basal forebrain (Llorens-Cortes et al., 1984; Grafe et al., 1985). There is a 33–43% reduction of Leu-Enk in pallidum with no change in other brain regions (Taquet et al., 1985). M-Enk immunoreactivity is markedly reduced in the lateral SN reticulata (Waters et al., 1988) without decrease in SN zona compacta and pallidum (Grafe et al., 1985; Zech and Bogerts, 1985; Graybiel et al., 1990). M-Enk binding sites are normal (Llorens-Cortes et al., 1984) or increased in the striatum (Rinne et al., 1983).

Substance P (SP)

SP that is highly concentrated in SN and the inner pallidum and neurons of the pontomesencephalic tegmentum (Halliday et al., 1990c) has an excitatory effect on dopaminergic neurons (cf Glowinski et al., 1980). The PD brains shows a 30–40% decrease in SP in SN and pallidum without essential changes in cortex, hippocampus striatum, and hypothalamus (Tenovuo et al., 1984; Beal and Martin, 1986). No decrease of SP-immonoreactivity in SN or pallidum was observed in PD, AD, and Guam-PDC (Grafe et al., 1985; Zech and Bogerts, 1985; Graybiel et al.,

1990), but Tenovuo et al. (1990) reported significant reduction of SP immunoreactivity in internal pallidum, in SN zona compacta and reticulata, and in the NBM in PD. Halliday et al. (1990b) observed mild reduction of SP^+ neurons in SN zona reticulata. Since the nigrostriatal dopaminergic cells innervate striatal SP-ergic neurons (Kubota et al., 1986), thus increasing their synthetic activity (Li et al., 1987), reduced dopaminergic transmission in PD may lead to diminished function of striopallidal SP^+ neurons, resulting in reduced SP-IR in the inner pallidum (Tenovuo et al., 1990). Recent studies suggest that SP-ergic neurons have an excitatory influence on dopaminergic nigrostriatal cells, whereas the latter have an excitatory mode of action on striatal SP-ergic neurons that is mediated via the D_2 receptors (Beckstead, 1987). Factors decreasing dopaminergic stimulation of the striatum have been shown to reduce the levels of SP immunoreactivity in the striatonigral terminals in SN (Tenovuo et al., 1990). Whether this reduction of nigral SP immunoreactivity is caused by depletion of SP stores as a compensatory mechanism or directly by reduced synthetic activity in these neurons remains to be elucidated. Recent immunohistochemical studies in PD showed a severe decrease in the number of SP^+ neurons and fibers in the brainstem, particularly in the SZ zona reticulata, in PPNc, in nucleus raphe obscurus, in dorsal motor vagal nucleus, and reticular formation of medulla (Table 8). This decrease is often associated with LBs in immunohistochemically identified neurons in these areas, which may also swell or have other degenerative changes indicating direct effect by the disease process (Halliday et al., 1990b).

In AD and PD + AD, SP is decreased by 30–57% in neocortex and hippocampus (Davies et al., 1980; Grafe et al., 1985; Beal and Martin, 1986), and SP immunoreactivity in globus pallidus and SN is increased (Constantinidis et al., 1988). Other authors found no decrease in SP immunoreactivity in cerebral cortex of AD and Down's syndrome (Yates et al., 1983).

Somatostatin (SS)

In both PD and AD conflicting results have been published for this peptide associated with GABA and its synthetic enzyme (GAD): In AD, reduced concentrations of SS (25–68%) have been reported in the cortex (Davies et al., 1980; Perry et al., 1981; Rossor et al., 1984). It is associated with reduced SS immunoreactivity in cortex (Beal et al., 1986) and in the basal nucleus and amygdala (Candy et al., 1985) and decrease in SS receptors in cerebral cortex (Beal et al., 1985,1986), but not in basal ganglia and NBM (Candy et al., 1985). SS-positive neurons appear dystrophic in temporal cortex and hippocampus (Chan-Palay, 1987) with distortion and depletion of immunoreactive fibers, but preserved neuronal density, in parietal cortex (Kowall and Beal, 1988). Other studies, however, showed no reduction of SS concentrations in cortical biopsies of AD (Bowen, 1990), and no reduction of SS immunoreactivity was seen

in the cortex of AD brains postmortem (Arai et al., 1984b; Candy et al., 1985; Whitford et al., 1988) and in biopsies (Francis et al., 1987). Also, no change in GAD activity was found when AD and controls were carefully matched for agonal state (Reinikainen et al., 1988b). On the other hand, Terry et al. (1990), in a series of AD subjects, saw significant correlations among Blessed dementia score, SS immunoreactivity, and density of neuritic plaques in parietal cortex. Decreased SS immunoreactivity (by 30–60%) has been reported in the cortex and hippocampus of demented PD subjects with cortical AD changes and in PD + AD (Epelbaum et al., 1983; Beal et al., 1988), but not in nondemented PD patients (Allen et al., 1985). On the other hand, Whitford et al. (1988) saw no significant changes of cortical SS immunoreactivity and high-affinity SS binding in frontal or temporal cortex of both AD and PD, and SS receptor density is unchanged in the cortex even of demented PD cases (Epelbaum et al., 1988). In contrast to normal, or even increased, SS concentrations in the striatum and nucleus accumbens in Huntington's disease (Beal and Martin, 1986), in PD, SS is either unchanged in the basal ganglia (Epelbaum et al., 1983; Epelbaum et al., 1988) or shows severe reduction or absence of SS immunoreactive cells and fibers (Forno et al., 1985). These data suggest a complex significance of SS deficiency.

Neuropeptide Y (NPY)

In PD, the number of NPY immunoreactive neurons and fibers in the medulla is significantly reduced, most severely in regions that contain monoamine-synthesizing cells; many of these neurons show degeneration or contain LBs (Halliday et al., 1990b). NPY is colocalized with SS in cortical neurons (Köhler et al., 1987; Gaspar et al., 1987; Chan-Palay, 1987; Kowall and Beal, 1988), and both coexist in neuritic plaques (Armstrong et al., 1989). In AD, reduction of NPY and NPY immunoreactivity has been observed in many brain regions (Beal et al., 1985,1986; Chan-Palay et al., 1985,1986); the loss of cortical NPY is equivalent to or much less severe than the decrease of SS (Foster et al., 1986; Beal et al., 1986,1988; Dawbarn et al., 1986), whereas Francis and Bowen (1989) saw no reduction of NPY concentrations in postmortem AD brain.

In demented PD subjects, despite a marked decrease in SS concentration, no or only mild decrease in cortical NPY immunoreactivity was observed (Beal et al., 1988). Similar dissociation between SS and NPY immunoreactivity has been reported in the cortex (Allen et al., 1985) and in hippocampus of PD-dementia, i.e., demented PD subjects with cortical AD pathology (Chan-Palay, 1987; Chan-Palay et al., 1989).

Other Peptides

Bombesin concentrations are mildly reduced in the caudate nucleus and external pallidum of PD brain (Bissette et al., 1985). Corticotropin-releasing factor (CRF) is reduced in cerebral cortex of PD brain (Dubois et

al., 1985; Whitehouse et al., 1987), but much more in AD, in which significant reduction by over 40% is seen in the neocortex (Bissette et al., 1985), although Kelley and Kowall (1989) reported preservation of neurons containing CRF in AD.

The following peptides have not been found to decrease in any region of the PD brain: dynorphin, vasopressin (VP), vasoactive intestinale peptide (VIP), galinin, thyreotropic hormone (TRH), and adrenocorticotropic hormone (ACTH) (cf Agid et al., 1987,1990). Neurotensin concentrations are unchanged in PD brains, except for a moderate reduction in the hippocampus (Bissette et al., 1985), although a dramatic decrease of neurotensin receptors is seen in the SN, probably as a result of loss of dopaminergic cells (Sadoul et al., 1984; Chinaglia et al., 1990). Similar data are reported for AD: VIP is either unchanged (Candy et al., 1983; Rossor et al., 1984) or mildly reduced (Arai et al., 1984b), and most of the other peptides, such as neurotensin, galinin and VP, are also normal (Yates et al., 1983; Nemeroff et al., 1989; Ferrier and Leake, 1990). Reduction in VP neurons in the suprachiasmatic nucleus without cell loss in supraoptic and paraventricular hypothalamic nuclei are seen in aging and AD (Swaab et al., 1986; Goudsmit et al., 1990); for PD, to the best of our knowledge, no data are available. In summary, the most important changes of neuropeptides in PD are:

1. In SN and pallidum: decrease of SP, M-Enk and CCK-8;
2. In the neocortex and hippocampus: variable decrease in SS and NPY, which may or may not be related to dementia.

In AD, the most important changes of peptides are:

1. In neocortex and hippocampus: decrease in SS and variable decrease in NPY and CRF that could be related to cortical pathology;
2. In NBM: increase in SS;
3. In SN and globus pallidus: mild increase in SP.

The latter could be related to cortical pathology and may induce mild dopamine deficiency in AD (Constantinidis et al., 1988).

Both the causes and the significance of the various neuropeptide deficiencies detected in the PD brain remain obscure, and the crucial question of whether these changes are primarily metabolic in origin, inducing dopamine deficiency, or are secondary to degeneration of the nigrostriatal dopaminergic neurons cannot be answered based on the findings from MPTP-treated monkeys (Taquet et al., 1987), although a variety of neuropeptide changes have been observed in lesioned animals (Allen et al., 1986; Agid et al., 1987). There is a large literature on the effects of dopamine lesions on the mRNAs for various peptides and for GAD in the striatum, suggesting close functional interactions and a dynamic interplay between the dopaminergic and peptidergic systems

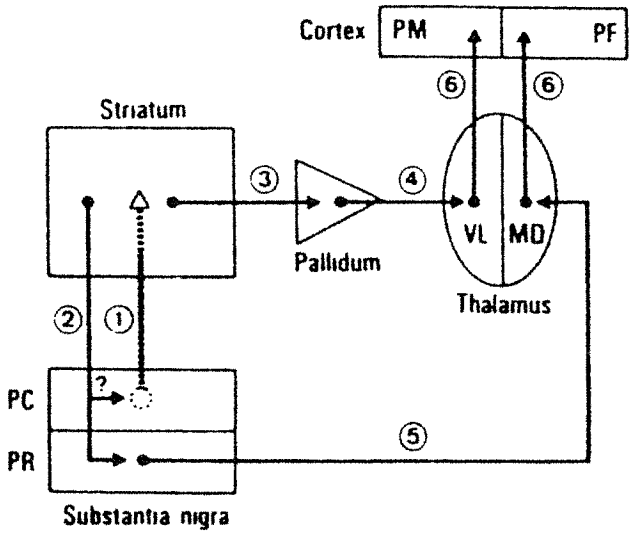

Fig. 4. Basal ganglia connections in Parkinson's disease. The dopaminergic nigrostriatal system (1) is severely damaged, whereas the striatal output systems, e.g., the striatonigral (2), striatopallidal (3), pallidothalamic (4), and thalamocortical projections (6), leading to the premotor (PM) and prefrontal cortex (PF), and the parallel striatonigrothalamocortical loop (5), projecting to the prefrontal cortex, seem to be intact. PC, PR = substantia nigra, pars compacta and reticulata; VL, MD = ventromedial, mediodorsal thalamic nuclei. Modified from Agid et al. (1990).

(Hornykiewicz, 1989; Reid et al., 1990), but the clinical implications of peptide deficiencies in PD are still poorly understood.

Goto et al. (1989), in PD, AD, and Guam PDC, did not observe any decreased immunoreactivity for SP and M-Enk, with strong immunoreactivity of the striatonigral afferent SN fibers for both substances in these disorders, suggesting that the corresponding peptidergic afferents are intact. Moreover, no reduction in immunoreactivity for calcineurin, a marker of striatal efferent axonal terminals, has been observed in the striatum of subjects with PD, AD, and Guam PDC (Goto et al., 1990). These data and the demonstration that in the PD brain both the synaptic organization (Forno and Norville, 1984) and the internal structure and neuronal organization of the striatum are preserved, even in advanced stages of the disease (Graybiel et al., 1990), suggest that the major striatal output system remains intact (Albin et al., 1989; Graybiel et al., 1990). If the efferent circuits from the basal ganglia toward the cerebral cortex are indeed preserved by PD (Fig. 4), restoration of dopaminergic transmission by levodopa substitution should logically permit functioning of

these extrapyramidal loops (Agid et al., 1990). By contrast, in striatonigral degeneration, a multisystem disorder, damage to the lateral and caudal putamen is associated with loss of calcineurin-immunoreactivity in the lateral SN zona compacta, suggesting the secondary nature of its degeneration as a result of primary striatal damage (Goto et al., 1990).

PATHOGENETIC CONSIDERATIONS

Progressive degeneration of the nigrostriatal dopaminergic system is the main characteristic of PD responsible for the classic motor symptoms of the disorder, which has been largely confirmed by the consequences of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) intoxication and the large number of its animal models (cf Langston and Irwin, 1989; Jenner and Marsden, 1990). In addition to the dopaminergic nigrostriatal loop representing the principal at-risk system in PD, a variety of other nonnigrostriatal neuronal systems are involved (*see* Table 9), inducing a multimediator dysfunction attributable to neuronal loss or degeneration, reduction of synthetic capacity of the remaining neurons, disorders of transport, and other compensatory mechanisms. These changes, thought to have modulatory effects on locomotor, behavioral, cognitive, autonomic, and other functions, often complicate the classic picture of PD, particularly in later stages of the disease.

The reasons for the widespread but selective nature of neuronal loss and degeneration within the brainstem in PD remains unclear, since many of the degenerating neurons are not pigmented, e.g., noradrenergic and serotonergic, SP- and NPY-containing cells (Halliday et al., 1990a), and not all melanin-containing neurons appear prone to degeneration. In addition, not all of the degenerating brainstem neurons have been shown to contain LBs, e.g., the SP^+ neurons in the lateral reticular formation or serotonin-synthesizing neurons in the median raphe nucleus lack this cytoskeletal lesion suggested to be an indicator for neuronal degeneration (Halliday et al., 1990b). LBs are cytoplasmic neuronal inclusions composed of intermediary-type filaments that are suggested to result from pathologic phosphorylation of neurofilaments with consecutive ubiquitination that may reflect fruitless attempts at proteolytic degradation of abnormal cytoskeletal proteins assembled in the perikaryon (Bancher et al., 1989; Jellinger, 1990b). They show a wide distribution, affecting many subcortical nuclei related to a wide variety of neuromediators, spinal cord, sympathetic ganglia, and, less frequently, cerebral cortex, parasympathic myentric plexuses, and adrenal medulla (cf Jellinger, 1989). However, the distribution of the LBs does not coincide with the pattern of neuronal degeneration in most cases of PD. Although LB in catecholaminergic neurons show positive reaction with TH antisera, suggesting that TH enzyme activity is preserved in these neurons or may play a role in the formation of these inclusions (Na-

Table 9
Subcortical Ascending Systems in Parkinson's Disease
(modified after Beal et al., 1988; Agid et al.; Halliday et al., 1990)

Neuronal system	Reduction vs controls %
1. *Mesocortical dopaminergic system*	
VTA: loss of melanin+. TH-immunoreactive neurons	40–86
Ventral mesencephalon: dopamin loss	
loss of TH activity	75
Limbic areas and neocortex: dopamine loss	40–60
2. *Noradrenergic system*	
Locus ceruleus: neuronal loss	30–90
Motor vagal nucleus: neuronal loss (TH-IR, SP-IR)	5–77
Supraoptic, paraventricular nuclei: cell loss	0
Neocortex, limbic areas: norepinephrine loss	40–75
3. *Serotonergic system*	
Dorsal raphe nucleus: neuronal loss	24–60
Striatum, neocortex: serotonin loss	20–60
Striatum, neocortex: 5-HT S-1, S-2 binding sites	reduced
4. *Cholinergic system*	
Nucleus basalis of Meynert: neuronal loss	32–93
Neocortex, hippocampus: ChAT, AChE loss	50–60
Neocortex, hippocampus: nicotinic receptors	30–55
Nucleus tegmenti pedunculopontinus: neuronal loss	36–57
Westphal-Edinger nucleus: neuronal loss	54
5. *Peptidergic systems*	
Cholecystokinin—Immunoreactivity in s.nigra	30–40
in other brain regions	0
Met-enkephalin—nigra, putamen, pallidum	50
Substance P—nigra, globus pallidus	30–40
immunoreactivity nigra, pallidum	0
brainstem nuclei, cell loss	57–85
Somatostatin: cortex, hippocampus (PD + AD)	30–60
Neuropeptide Y—medulla: neuronal loss	70
immunoreactivity: cortex, hippocampus (PD + AD)	10–30

kashima and Ikuta, 1984), most of the degenerating neurons in the brainstem have lost their TH-immunoreactivity, indicating loss of TH enzyme activity and show decreased TH messenger RNA (Javoy-Agid et al., 1990; Hirsch et al., 1988; Graybiel et al., 1990). The same is true for other mediator-specific neurons that show LBs, other degenerative changes, and loss of immunoreactivity for the synthesized mediator

(Halliday et al., 1990a,b). The molecular basis and pathogenesis of this region-specific degenerative process, affecting not all neurons of a particular nucleus containing one or more specific neuromediators or harboring LB, remain open for further elucidation.

Immunohistochemical studies of the human brainstem using monoclonal antibodies against monoamine oxidase (MAO) A and B and polyclonal antibodies against TH (Konradi et al., 1988; Westlund et al., 1988) showed a strong TH-IR, but almost negative IR, for both MAO A and B in the neurons of the SN compacta and the nigrostriatal fibers, both preferentially involved in PD; strong TH-IR, but mild IR, for both MAO A and B was seen in the mesencephalic VTA and reticular formation, also considerably damaged in PD. Strong IR for both TH and MAO A was seen in the noradrenergic LC, and in the cholinergic oculomotor complex and PPNc, both involved in PD. MAO B was located mainly in the TH-negative serotonergic cells of the DRN, severely involved in PD. In the medulla, the solitary nucleus has coexpression of MAO A and TH, and the noradrenergic dorsal vagal nucleus, variably involved in PD, shows coexpression of TH and MAO B. The large serotonergic neurons of reticular formation, reacting with antibodies to all three enzymes (Fig. 5), are severely affected in PD (Halliday et al., 1990a). The astroglia in all regions are strongly positive for both MAO A and B, more intensively for MAO B. These data appear of interest in view of neuronal losses in selective cell groups of the brainstem in PD and with regard to the MPTP model of PD, since MPTP is oxidized to the neurotoxic 1-methyl-4-phenylpyridinium ion (MPP^+), probably by MAO B in glial cells (cf Brooks et al., 1989). In both human and primate brain, MAO B is primarily localized in serotonergic neurons (Westlund et al., 1985,1988), which are not affected by MPTP, but are affected in human PD. However, it is almost absent in DA-ergic nigral neurons that are selectively destroyed in both PD and its MPTP model in various species (Kopin and Schoenberg, 1988). There are some similarities and dissimilarities in the histopathological pattern of human PD and chronic MPTP syndrome in human and primates: A human case of MPTP-induced parkinsonism showed destruction of the SN zona compacta with one questionable LB (Davis et al., 1979). In subhuman primates, there is a constant diffuse neuronal loss in the areas A-8 and 9, greatest in the ventral and lateral parts of SN compacta, less in A-8 and VTA (A-10) (Schneider et al., 1987; Ricaurte et al., 1987; German et al., 1988a; Gibb et al., 1989b; Albanese et al., 1990), that is similar to the lesions in human PD. In the marmoset, additional damage involves the arcuate nucleus of hypothalamus (A-12) and dorsal hypothalamus (A-13), rather preserved in human PD (Matzuk and Saper, 1985), the periventricular region (A-14), and nucleus of stria terminalis region (A-11), although the LC, DRN, and cholinergic substantia innominata are preserved (Gibb et al., 1989). In squirrel monkeys, damage to LC is seen in 58%, more often in aged than in young ones, with occasional eosinophilic neuronal inclusions in SN, LC, and NBM, near the

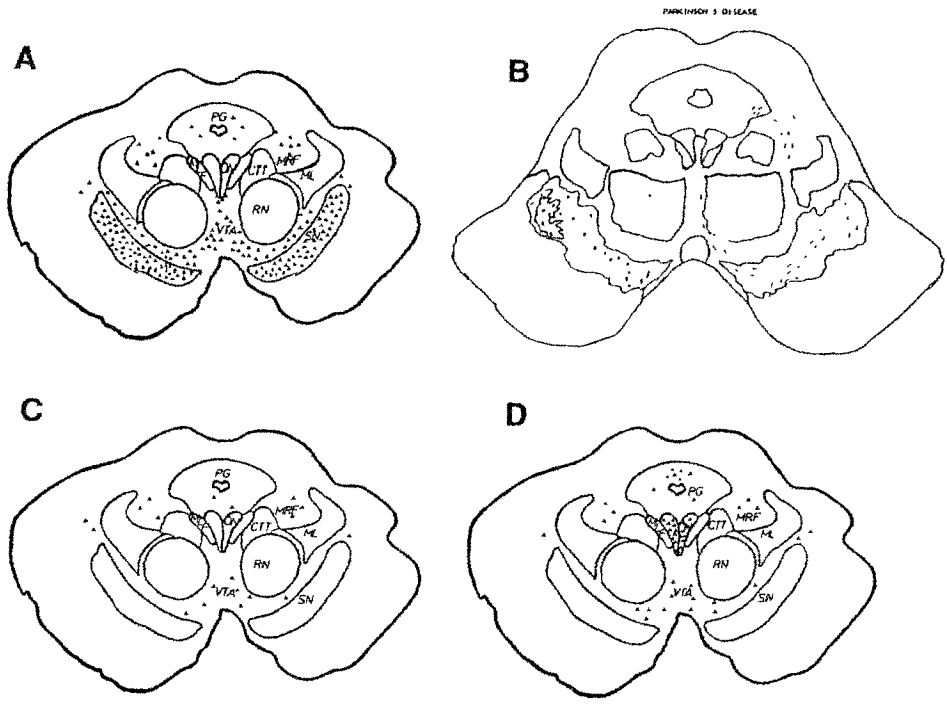

Fig. 5. Schematic distribution of neuronal immunostaining in human midbrain with antibodies to tyrisine hydroxylase (TH) in (A) normal and (B) PD brain, and to (C) MAO B and (D) MAO A in normal human brain.

dorsal motor vagal nucleus, and in amygdala (Forno, et al., 1986; Forno, 1990). These inclusions have been suggested to resemble LBs, but their ultrastructure (Forno et al., 1988) and immunohistochemistry (negative reactions for tau, MAP, ubiquitin) differ from typical LB (Forno, 1990). Although in chronic experimental MPTP syndrome in primates the location of damage in the midbrain (nigrostriatal system) is similar to that in human PD, the absence of typical LBs and the apparent preservation of most of the noradrenergic, serotonergic, and cholinergic cell groups of the brainstem with different pathobiochemistry (cf Hornykiewicz et al., 1989; Nagatsu, 1990) represent major differences between the two conditions.

Another open question is the relation of PD to aging. There is considerable overlap between PD and either aging or AD with respect to morphology, cytoskeletal pathology, and neurochemical deficits. In both PD and AD the degenerative lesion and cytoskeletal pathology affecting several ascending neuromediator-specific neuron systems are similar in quality and distribution, but highly variable in intensity (cf Jellinger, 1989; 1990a–c). The available data, however, allow suggestion that PD and AD are different in the primary locus of the basic process. Recent morphologic studies in AD, showing correlations between the intensity

and topographic pattern of the cell depletion in some subcortical nuclei, e.g., LC and NBM, and both neuronal loss and the density of Alzheimer lesions in their cortical projection fields, suggest that degeneration of such nuclei may occur as a consequence of primary neuronal damage in the cortex through anterograde or retrograde mechanisms (Allen et al., 1988; Burke et al., 1988; Zweig et al., 1989b; Jellinger, 1989). In PD, to the best of our knowledge, no such cortico–subcortical relation of morphologic changes has been observed so far. In this disorder severe depletion of subcortical nuclei may occur without impressive cortical damage or Alzheimer pathology. These facts do not support the contention that degeneration of subcortical nuclei is secondary to cortical lesions, but are most compatible with the suggestion of an independent or "parallel" degeneration of both subcortical and intracortical neuronal systems in PD. The same is true for the relations between the degenerating dopaminergic nigrostriatal loop and neuronal damage outside, since these nonnigrostriatal lesions responsible for the aggravation of the disease are not situated downstream from the degenerating nigrostriatal neurons, but are rather "in parellel" with the dopaminergic lesion. In conclusion, the molecular basis, the time-course, and the mutual pathogenetic interrelations of neuronal degeneration involving different subcortical systems in PD are unknown, and their pathophysiology, clinical consequences, and therapeutic implications are still poorly understood. Clarification of these problems is a major challenge for modern neurosciences.

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