Neurotransmitters in the Basal Ganglia

Edith G. McGeer, William A. Staines and Patrick L. McGeer

ABSTRACT: The literature is reviewed on the afferents and efferents of the caudate/putamen, globus pallidus and substantia nigra, and on the neurotransmitters occurring in the various tracts. Emphasis is placed upon the diverse roles played by GABA and glutamate as transmitters in motor pathways and upon the probability that the substantia nigra pars reticulata plays a pivotal role in the output of the basal ganglia. Excessive stimulation of the projection from the pedunculopontine tegmental area to the substantia nigra is shown to cause destruction of dopaminergic neurons in the latter nucleus, suggesting another possible mechanism for cell death in Parkinson's disease.

RÉSUMÉ: Nous revisons la littérature sur les afférences et efférences du caudé/putamen, globus pallidus et substantia nigra, et sur les neurotransmetteurs de ces différentes voies. Nous insistons sur les divers roles du GABA et du glutamate comme transmetteurs des voies motrices et sur la probabilité que la substantia nigra pars reticulata joue un rôle crucial dans l'output des noyaux gris centraux. Une stimulation excessive de la projection de l'aire tegmentaire pédonculo-protubérantielle à la substance noire cause une destruction des neurones dopaminergiques dans ce dernier noyau, suggérant un autre mécanisme de mort cellulaire dans la maladie de Parkinson.

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Classical neuroanatomists attempting to portray the interconnections of the extrapyramidal motor system came up with the complicated diagrams which are familiar to readers of classical textbooks. Biochemical neuroanatomists tend to reduce the complexity by showing only those tracts for which the neurotransmitter has been chemically identified. Such diagrams put undue emphasis on a few pathways. In this review we will attempt to describe the neurotransmitters of the principal nuclei of the extrapyramidal motor system in the context of the numerous tracts which have been defined by classical neuroanatomical methods and by the more recent application of axonal transport tracing techniques. The diagrams will still be oversimplified because some of the very minor tracts will be omitted and the topographical patterns which seem characteristic of many of these systems will be ignored. Possible species differences are also ignored; these are more likely to be quantitative rather than qualitative.

A complicating factor in biochemical neuroanatomy is the large number of putative transmitters in the central nervous system. These can, however, be grouped into three major classes (Table 1). In general the amino acid neurotransmitters are present in micromoles/gm tissue, the amine neurotransmitters in nanomoles/gm tissue and the peptides in picamoles/gm tissue. Although glutamate, aspartate and glycine are present in many compartments other than the neurons they serve, it still seems probable that the amino acids must account for a very high proportion of the neurons of brain. The other neurotransmitters may, of course, by their modulatory actions, have qualitative importance far outreaching their probable quantitative importance. It is clear, however, that the probable quantitative importance of the various neurotransmitters in brain is not well correlated with the priorities that have been given in research or with the amounts of knowledge accumulated. Thus, a major part of neurotransmitter-related research in the last 25 years has been directed towards the aromatic amines and the peptides are now enjoying a tremendous surge in popularity. Considerable knowledge of the neuroanatomy of these systems has been accumulated and most speculation as to the relation of disease or function to specific neurotransmitters has been focused on the amines and peptides. Although the amino acids are favorites of the neurophysiologists — since they seem to act by classical ionic mechanisms — they have been neglected until relatively recently by the neuroanatomists, neuropsychologists and clinically oriented neuroscientists.

Most of the neurotransmitters listed in Table I are present in the extrapyramidal system, many of them in relatively high

Table 1: Approximate levels in rat brain of various neurotransmitters (in Picamoles per gram)

AMINO ACIDS (70-90% of central neurons)			AMINES (5-20% of central neurons)	
*Glutamate	14,000,000)	Glu/Asp	*Acetylcholine	25,000
Aspartate	4,000,000)		*Dopamine	6.500
*GABA	2,500,000		*Noradrenaline	2,500
*Glycine	2,000,000		*Serotonin	2,500
			*Histamine	1,000

PEPTIDES (Partial List) (less than 5-10% of central neurons)			
*CCK	470	LHRH	7
*Met-enkephalin	350	*Dynorphin	4
*Substance P	100	Bradykinin	<1
*VIP	40	ACTH	<1
*Somatostatin	30	α-MSH	<1
*Neurotensin	12	*TRH	<0.3
		Bombesin	<0.2

* Present in the basal ganglia

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concentrations compared to other brain regions. In discussing where these neurotransmitters may fit into the wiring diagrams of the extrapyramidal system, these will be considered in terms of the efferents and afferents of the caudate/putamen (CP), of the globus pallidus (GP) and of the substantia nigra (SN).

Projections of the Caudate/Putamen (See Figure 1)

The projections of the CP are simple since there appear to be only three, or possibly four. Well established tracts are those to the GP, the entopeduncular nucleus (EP) and the SN (Dray, 1979); Beckstead (1983) and Nauta and Cole (1978) indicate a minor projection to the subthalamus. The projection from the CP to the SN is particularly massive and probably ends mainly in the zona reticulata (SNR) (Hattori et al., 1975). As many as 65-70% of the neurons of the CP may project to the SN and at least two morphologically distinct types of striatonigral neurons have been shown (Bolam et al., 1981).

Five neurotransmitters have so far been implicated in these projections. There is excellent evidence for enkephalin as a neurotransmitter in projections from the CP to the GP (Brann and Emson, 1980; Del Fiacco et al., 1982; Somogyi et al., 1982; cf Haber and Elde, 1981). The CP contains a dense network of met-enkephalin fibers and terminals (Yang et al., 1983) so there may also be enkephalin interneurons.

Substance P projections arise throughout the CP and seem to project, probably by collaterals, to all three other nuclei, i.e. to the GP, the EP and the SN (Brownstein et al., 1977; Jessel et al., 1978; Staines et al., 1980). In primates, the external segment (GP) shows relatively little staining for substance P, with the staining being, progressively, much more dense in the internal segment (EP) and in the SN (Beach and McGeer, 1984; Haber and Elde, 1981). Substance P, enkephalin and acetylcholinesterase have all been found to occur in different, distinct patterns in the cat caudate, with more uniform patterns in the putamen (Graybiel et al., 1981). Islands of intense substance P-like immunoreactivity have also been found in human and baboon caudate (Beach and McGeer, 1984).

Dynorphin distributions are similar to those of substance P (Vincent et al., 1982a) and this endorphin may occur in similar projections to all three nuclei; that to the SN is the best established (Vincent et al., 1982b).

GABA occurs in a massive projection from the neostriatum to the SN but it is controversial as to whether the greater part of this projection arises in the GP, the tail of the caudate or at the border between the two (for review see E.G. McGeer et al., 1982). There are also GABA projections from the CP to the GP and from the CP to the EP. The GABA projections to the GP may be partly by collaterals of those to the SN.

Choleocystokinin (CCK) may also be present in a projection to the SN since injections of the neurotoxin, kainic acid, into the rat CP lead to losses of CCK in the SN as well as the CP (Emson et al., 1980; see also Table 3).

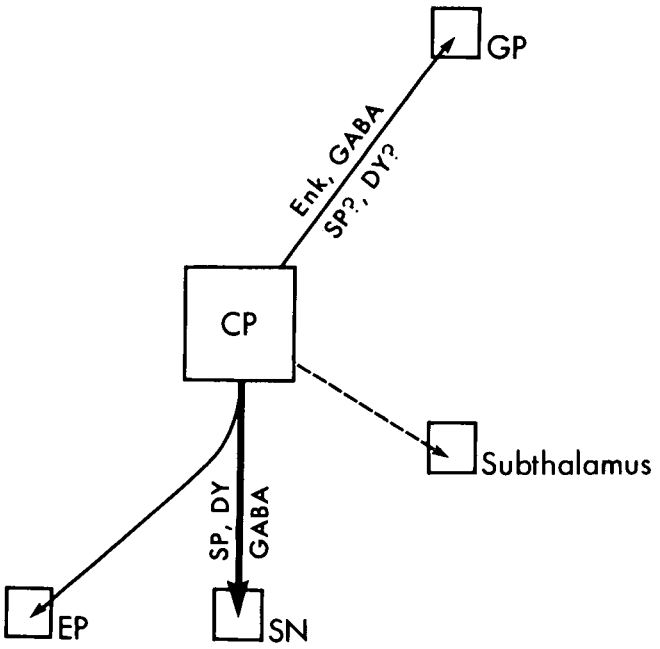

Figure 1 — Projections of the Caudate/Putamen. In this and subsequent diagrams, relative sizes and locations of the nuclei are ignored and a given tract may involve more than the neurotransmitters shown. For the topography of the projection to the GP, see Wilson and Phelan (1982) and Chang et al. (1981), and for the morphology of cells projecting to the SN, see Smith et al. (1981) and Tulloch et al. (1978). Enk, enkephalin; SP, substance P; Dy, dynorphin; other abbreviations as in text.

Afferents to the Caudate/Putamen (see Figure 2)

The most massive inputs come from the thalamus, the cortex and the SN. There are also minor inputs from the locus coeruleus, the dorsal raphe, the amygdala, probably the mammillary body, pedunculopontine tegmental nuclei and, possibly, the reticular formation and subthalamus. The projections from the SN and the raphe are both reported to be partly to the contralateral CP but the same cells do not project bilaterally (Loughlin and Fallon, 1982). The prefrontal and SN projections to the CP are convergent (Beckstead, 1979).

A major unsolved question in the biochemical neuroanatomy of the extrapyramidal system is the nature of the neurotransmitter(s) in the massive thalamostriatal tract. Despite some reports, it appears highly unlikely that this tract is served largely by glutamate, aspartate or acetylcholine (P.L. McGeer et al., 1982; McGeer et al., 1977).

The relatively minor projections from the dorsal raphe and locus coeruleus are parts of the well-known and diffuse serotonergic and noradrenergic systems of the brain. A second (excitatory) neurotransmitter may be involved in the raphe-striatal tract (Park et al., 1982).

There is some lesion evidence indicating that histamine innervation of the CP arises in the mammillary body and possibly also in the reticular formation (Barbin et al., 1977).

The well-known dopamine system from the SN to the CP also gives off some collaterals in the GP. Although dopamine probably accounts for about 85-95% of the massive nigrostriatal tract, there does seem to be at least one other neurotransmitter involved (Connor, 1975; Deniau et al., 1978b; Fibiger et al., 1972; Hedreen, 1978; van der Kooy et al., 1981). A peptide worth consideration for a minor role in this tract is neurotensin. Neurotensin immunoreactive cells are found in the SN (Jennes et al., 1982; Uhl et al., 1979), there is a dense mosaic of positive fibers and terminals in the striatum (GP > caudate > putamen) (Goedert et al., 1983), and neurotensin facilitates dopamine release in

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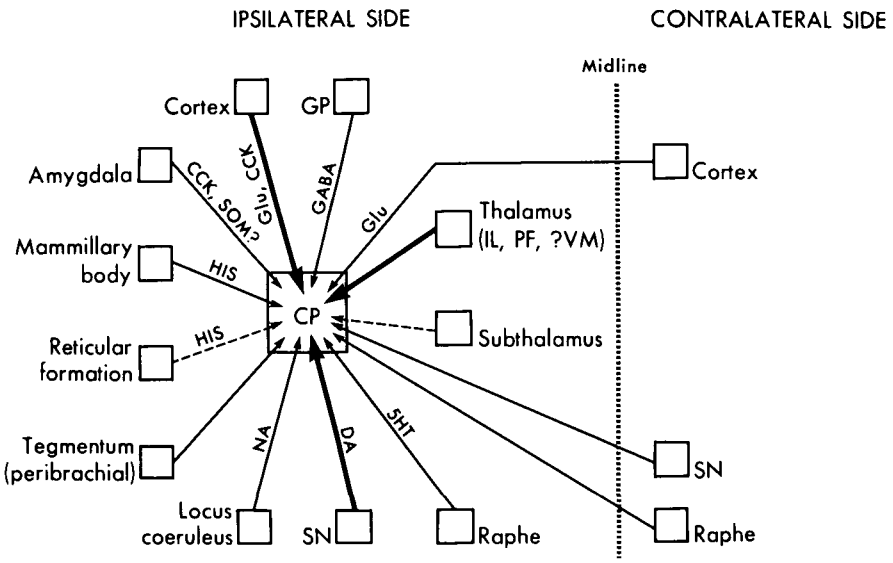

Figure 2 — Afferents to the Caudate/Putamen. (a) GP to CP (Staines et al., 1981; Arbuthnott et al., 1982a,b; Buchwald et al., 1981; Chung and Hassler, 1982; Jayaraman, 1983 (topography)). (b) Tegmental area to CP (Saper and Loewy, 1982). (c) Cortex to CP (Hedreen, 1977; Yeterian and van Hoesen, 1978; Fallon and Ziegler, 1979; Oka, 1980; Donoghue and Kitai, 1981; Royce, 1982). (d) Thalamus to CP (From intralaminar (IL) and parafascicular (Pf) nuclei; projections from the ventromedial nucleus (VM) are controversial (Jones and Leavitt, 1975; van der Kooy, 1979; Veening et al., 1980; Herkenham, 1979; DiFiglia et al., 1978 (morphology); Sugimoto and Hattori, 1983 (collaterals to the subthalamus)). (e) Amygdala to CP (Royce, 1978; Kelley et al., 1982). (f) Raphe to CP (van der Kooy, 1979; Loughlin and Fallon, 1982). (g) Subthalamus to CP (sparse and may be to displaced GP cells, Ricardo, 1980; van der Kooy and Hattori, 1980). Glu, glutamate; HIS, histamine; NA, noradrenaline; 5HT, serotonin; DA, dopamine.

vitro from striatal slices (de Quidt and Emson, 1983). The levels are generally reported as relatively high in both the CP and SN although there is some variability in the available data (Goedert and Emson, 1983; Emson et al., 1982; Manberg et al., 1982; Uhl and Snyder, 1976).

It is also remotely possible that CCK may be involved in the nigrostriatal projection but the majority of the CCK innervation of the CP seems to come from the amygdala (30%) and the pyriform cortex and/or claustrum (70%) (Meyer et al., 1982).

The projection from the amygdala to the CP may also contain somatostatin. Other suggested sources of somatostatin innervation of the CP are the cortex, the periventricular nucleus of the hypothalamus and the tegmental area since somatostatin-positive cells have been reported in those locations (Takatsuki et al., 1981). Beal and Martin (1983) indicate that about half the somatostatin in the CP comes from external sources but not from the dorsal cortex, thalamus or brainstem. The other half of the somatostatin in the CP appears to be in perikarya which are probably intrinsic neurons (DiFiglia and Aronin, 1982; Finley et al., 1978; Graybiel et al., 1981). It has been estimated that 4-5% of striatal neurons in a rat contain somatostatin and these are distinct from the 4 to 5% which are intrinsic cholinergic neurons (Vincent et al., 1983a); some of the somatostatin cells also contain avian pancreatic polypeptide (APP)-like immunoreactivity (Vincent et al., 1982c). As seems to be the case for most neurotransmitters, there are anterior to posterior variations in somatostatin levels in all nuclei of the basal ganglia (Davies et al., 1981) and the staining of cells is found in patches in the CP (Chesselet et al., 1982; DiFiglia and Aronin, 1982).

The pallido-striatal tract appears to be GABAergic and to land largely on the somatostatin neurons. There are also, of course, many GABA interneurons in the CP, as well as some thyrotropin releasing hormone (TRH) perikarya (Spindel et al., 1981). Relatively little is known about the TRH system.

The massive projection from the cortex to the CP appears to use glutamate and/or aspartate — what we prefer to call a Glu/Asp system since it is sometimes difficult to distinguish the one from the other (although the evidence in this particular case favors glutamate as the neurotransmitter). This excitatory system innervates most of the neurons of the CP and there are similar cortical Glu/Asp projections to other subcortical areas related to motor control including the ventrolateral thalamus, the red nucleus, the basis pontis, the superior colliculus, the spinal cord and probably the SN and subthalamus (Figure 3).

The Glu/Asp projection to the CP comes mainly from the neofrontal, motor and pyriform areas of the ipsilateral cortex but there is some contribution from the contralateral cortex; this is one of the levels at which some integration between the hemispheres may occur (Leichnetz, 1981; Walker, 1983). Since many commissural pathways are also probably Glu/Asp, such integration is highly dependent upon these amino acid transmitters.

An interesting possibility suggested by work in other areas of brain is that adenosine receptors may be located on axon terminals of these excitatory Glu/Asp neurons and help regulate the output of the excitatory neurotransmitter (Goodman et al., 1983; Wojcik and Neff, 1983).

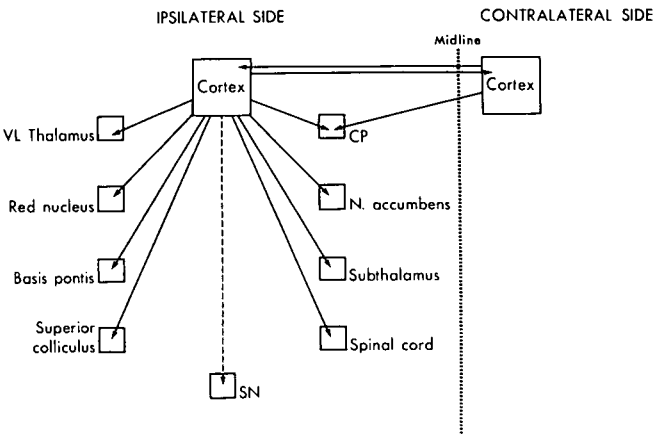

Figure 3 — Glu/Asp projections to some nuclei possibly or probably concerned in motor control. For reviews of the literature on these pathways see McGeer and McGeer, 1981; Walker, 1983.

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Afferents to the Globus Pallidus (see Figure 4A)

Two of the main afferents have been previously described and comprise inputs from the CP and from the SN. The input from the CP contains enkephalin and probably GABA; some substance P and dynorphin fibers may also occur. The projection from the SN certainly contains dopamine and may contain other substances.

Projections to the GP also arise in the subthalamus, the nucleus accumbens and, possibly, the tegmental area (see last page of text). The transmitter serving the tract from the subthalamus is still uncertain since it has been variously reported to use the inhibitory transmitter GABA or to be excitatory; this projection is believed to have collaterals to the SN and EP (Deniau et al., 1978a; van der Kooy and Hattori, 1980a). The projection from the nucleus accumbens — which may be considered a ventral extension of the CP — is to the ventral pallidum rather than the GP proper and seems to use GABA (see Figure 5).

Projections of the Globus Pallidus (see Figure 4B)

The GP projects mainly to the subthalamus (Kim et al., 1976) but also the EP, the SN (Hattori et al., 1975; Carter and Fibiger, 1978), the CP, the dorsal raphe and, rather sparsely, to the

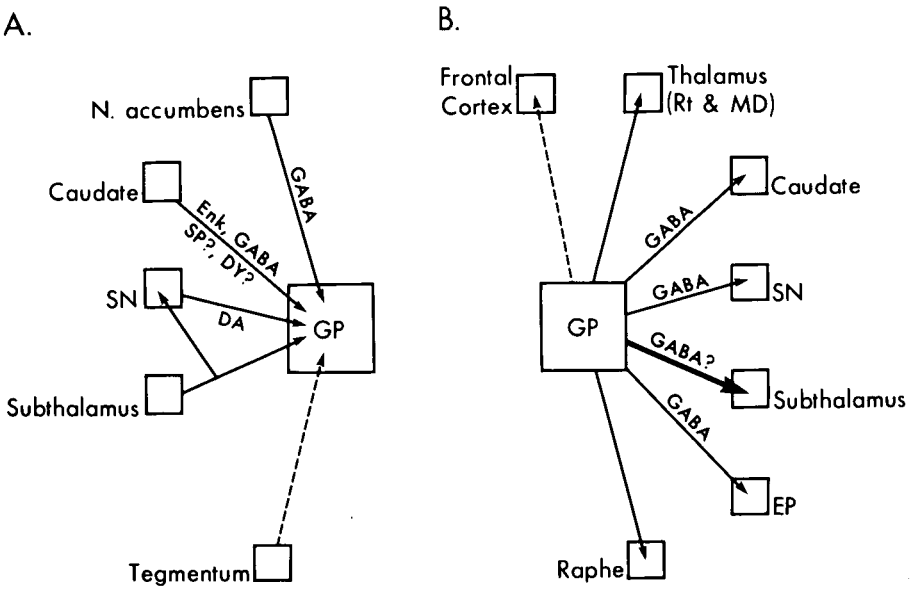

Figure 4 — Afferents to the Globus Pallidus (A) and Projections from the Globus Pallidus (B). Rt, reticular and MD, medial dorsal nuclei of the thalamus; other abbreviations as in Fig. 1.

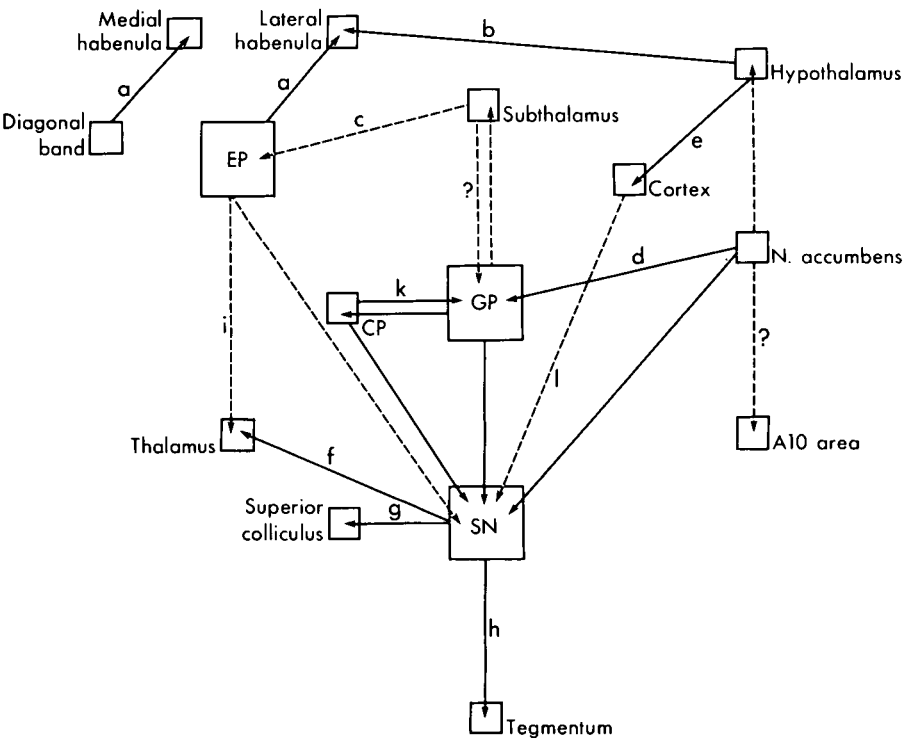

Figure 5 — Reported long axoned GABAergic tracts. Many references may be found in E.G. McGeer et al. (1982); McGeer and McGeer (1981). cf also: (a) EP to lateral habenula, Contestible and Fonnum (1983) who also report a GABA projection from the diagonal band of Broca to the medial habenula. (a,b) The projections from the rostral EP and the lateral hypothalamus to the lateral habenula apparently arise from both GABAergic and non-GABAergic cells (Araki et al., 1984b). (c) Subthalamus (SUT) to EP, Rouzaire-Dubois et al. (1983). (d) Scarnati et al. (1983). (e) Vincent et al. (1983b). (f) Starr and Kilpatrick (1981); no convergence of pallidal and nigral influences is observed within thalamic neurons (Ueki, 1983). (g) Chevalier et al. (1981a,b); double labelling studies indicate that the projection to the superior colliculus from the pars reticulata of the SN (and from the nearby zona incerta) are wholly GABAergic (Araki et al., 1984a). (h) Childs and Gale (1983), diffuse GABA projections to pedunculopontine nucleus and adjacent tissue of the pontomesencephalic tegmentum. (i) EP to VL thalamus; these projections are partially bilateral (Nakano et al., 1982; DeBellefeuille and Parent, 1982). (k) Both the GP to CP and CP to GP paths send some collaterals to the SN. (l) Scatton et al. (1982).

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reticular and medial dorsal nuclei of the thalamus and to the frontal cortex (Nauta, 1979a).

There have been claims of a pallidocortical cholinergic projection (Edstrom and Phillis, 1980; Kelly and Moore, 1980), but this projection arises from the magnocellular neurons of the substantia innominata (nucleus basalis of Meynert), the distribution of which overlaps the boundaries of the globus pallidus (and putamen). Another projection, from non-magnocellular cells of the GP proper, is limited to the frontal cortex (Ribak and Kramer, 1982); the neurotransmitter is unknown but may be GABA.

GABA is the only neurotransmitter yet definitively identified in any of the projections of the GP. The GP, like the EP and the SN, probably contains a very high concentration of GABAergic neurons. In histochemical studies in our laboratory aimed at identifying presumptive GABAergic neurons, some of the most beautiful staining was evident in these three nuclei (Nagai et al., 1983). These nuclei are also prominent in Figure 5 which shows almost all of the long axoned GABA systems which have been so far suggested in the literature. In addition, most of the nuclei shown in Figure 5 contain high concentrations of GABA interneurons. It is clear that GABA systems play a major role in motor control but act at many different levels.

A number of these pathways are believed to be extensively collateralized and some appear to converge. Thus, for example, the EP to the thalamus innervates the same ventromedial nucleus (Carter and Fibiger, 1978) that receives innervation from the SN (Clavier et al., 1976) and from the deep cerebellar nuclei (Herkenham, 1979; Sugimoto et al., 1981) and projects in turn to cortical regions which innervate the CP (Herkenham, 1979). In monkeys the EP also sends some fibers to the central median/parafasicular complex of the thalamus which also receives innervation from the ipsilateral superior colliculus and tegmental pedunculo-pontine nucleus, providing another point of possible convergence (DeBellefeuille and Parent, 1982).

Another point of interest in Figure 5, and Figures 6-7, is the many ties between nuclei of the motor system and those usually associated with the limbic system. Clearly the two are closely interwoven in many respects.

Afferents to the Substantia Nigra (see Figure 6)

The SN is the smallest of the nuclei of the extrapyramidal system which we are considering but seems nevertheless to have the most complicated wiring diagram. These involve a number of connections with the contralateral side which provide, with the bilateral cortical innervation of the striatum and the commissural Glu/Asp tracts, means for hemispheric integration. Major afferents to the SNR and zona compacta (SNC) which come, respectively, from the CP and the GP have already been discussed. There is also a projection from the nucleus accumbens to the SNC and from the midbrain tegmental area, most probably the pedunculopontine nucleus, to the SNR and SNC. The latter projection is bilateral, although the ipsilateral component is much heavier than the contralateral component. The SN also receives projections from the cortex, the lateral habenula, the parafascicular nucleus of the thalamus, the subthalamus, the amygdala, the raphe and the hypothalamus. All of these seem to be exclusively ipsilateral except for the hypothalamic afferents which are bilateral. However, those from the ipsilateral hypothalamus come from the anterior portion, while those from the contralateral come from the posterior regions. The transmitters for many of these afferents are unknown but some have been postulated.

Some of the probable transmitters in the tracts from the cortex, the CP, the GP and the raphe have already been mentioned, i.e.: from the raphe, serotonin; from the CP, substance P, GABA and dynorphin; from the GP, probably GABA; and from the cortex possibly glutamate and/or GABA (see Figures 3 and 5).

It has been said that some oxytocin and a few vasopressin fibers project to the SN from the hypothalamus (Nilaver et al., 1979; Sofroniew, 1980).

Some recent lesion studies in our laboratory indicate that at least part of the ipsilateral projection from the pedunculopontine nuclei (peribrachial area) may be cholinergic but that another neurotransmitter is probably involved in the bilateral projections. Cholinergic neurons are located diffusely in this general area (Kimura et al., 1981, 1984) and microinjections of the excitotoxin,

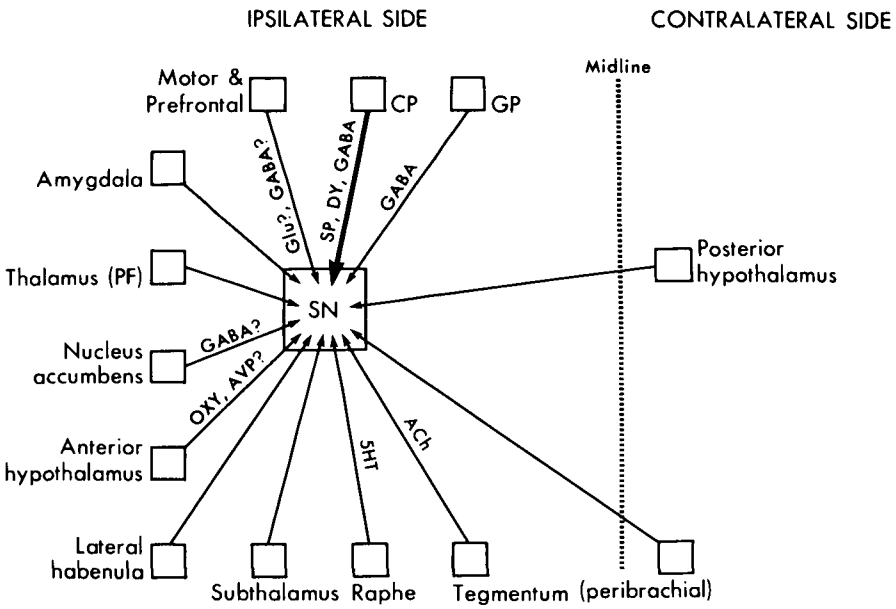

Figure 6 — Afferents to the SN. For references see Gerfen et al. (1982) and Saper and Loewy (1982). ACh, acetylcholine; OXY, oxytocin; AVP, vasopressin; other abbreviations as in Fig. 1.

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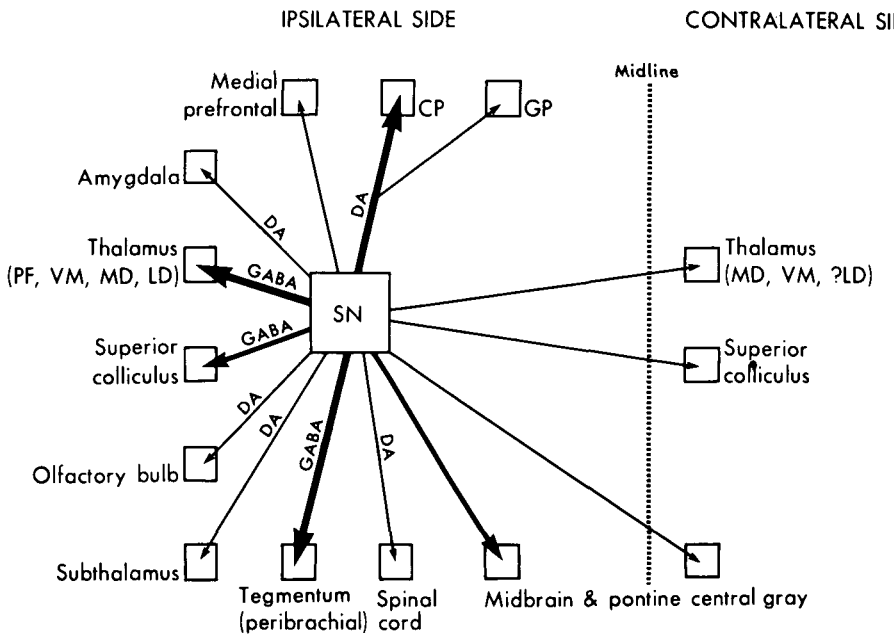

Figure 7 — Efferents from the SN. For references see Gerfen et al. (1982). PF, VM, MD, LD, parafascicular, ventromedial, medial dorsal and lateral dorsal nuclei of the thalamus; DA, dopamine.

kainic acid, caused local lesions which did not encroach upon the SN (or the midline) but which, nevertheless, resulted in significant decreases in both glutamate decarboxylase (GAD) and choline acetyltransferase (ChAT) levels in the ipsilateral SN. These enzymes were not affected in the contralateral SN or in either CP. Pretreatment with scopolamine abolished the changes in GAD without affecting those in ChAT (Table 2A). These results are consistent with an ipsilateral cholinergic projection from the injected region to the SNR, with the loss of GAD in the SNR being a secondary effect dependent upon overexcitation of this projection. Such an effect would be analogous to the loss of cortical and amygdala GABA neurons seen following injections of either kainic acid or folic acid into the substantia innominata area where the cholinergic innervation of cortex and amygdala arises (McGeer et al., 1983). The postulated mechanism for the loss of GAD in the SN is consistent with the reports that acetylcholine is markedly excitatory to cells in the SNR (Collingridge and Davies, 1981; Pinnock and Dray, 1982).

Such injections of kainic acid (or folic acid) also caused losses of dopamine cells in the SN (as initially reported by Ricciardi et al., 1981); these losses were partly bilateral as evidenced by measurements of tyrosine hydroxylase in the CP (Table 2B) and were not significantly affected by scopolamine. This suggests that the bilateral projection from this area innervates dopamine neurons of the SN and is served by some transmitter other than acetylcholine. One possibility is the excitatory peptide, neurotensin, since its levels are relatively high in the SN, the neurotensin binding sites are said to be on dopamine neurons (Palacois and Kuhar, 1981) and neurons straining for neurotensin have been found in the dorsal pontine tegmental area (Matsuzaki et al., 1981; Beitz, 1982). Substance P is another possibility since it is excitatory and ascending projections from this general area have been reported (Sakanaka et al., 1983).

It is tempting to speculate that abnormalities in these projections from the pedunculo-tegmental area to the SN may be involved in the etiology of some forms of Parkinsonism and, on this basis, further studies aimed at identifying the neurotransmitters in these projections and assessing their status in Parkinsonian brains seems worthwhile.

Almost certainly other transmitters are also involved in afferents to the SN. Histamine concentrations, histidine decarboxylase activity and high affinity glycine uptake are all relatively high in the SN, suggesting the possibility of afferents or internal neurons using these neurotransmitters. Pollard et al. (1978) indicated there were most probably histamine afferents to the SN but the origin was unknown.

Projections from the Substantia Nigra (see Figure 7)

The projections from the SN are equally complex. There is a vast literature on the massive projections to the CP and to the ventromedial nucleus of the thalamus. There are much less data

Table 2: Some enzyme levels (as percent of control) following injections of kainic acid or folic acid into the pedunculopontine tegmental area

A. In the Substantia Nigra

	ChAT		GAD	
	Ipsi	Contra	Ipsi	Contra
Kainic acid (KA) injected	51%*	86%	59%*	96%
KA after scopolamine	49%*	81%	97%	109%

B. In the Neostriatum

	Tyrosine Hydroxylase	
	Ipsi	Contra
Folic acid injected	74%*	92%
KA injected	64%*	82%*
KA after scopolamine	80%*	84%*

* Significantly different from control; the tyrosine hydroxylase values in the last two groups are not significantly different one from the other.

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on the massive but somewhat diffuse projection to the tegmental area. The SN also projects to the subthalamus, the parafascicular, ventromedial, medial dorsal and lateral dorsal nuclei of the thalamus, the amygdala, the olfactory bulb, the superior colliculus, the midbrain and pontine central grey and the spinal cord. The projections to the superior colliculus, various thalamic nuclei and the midbrain and pontine central grey are bilateral, with the ipsilateral innervation being the more massive in each case.

Only two neurotransmitters, dopamine and GABA, have so far been identified in projections from the SN. There are dopaminergic tracts to the CP, GP, amygdala (Meibach and Katzman, 1981), subthalamus (Brown et al., 1979; Miebach and Katzman, 1978), olfactory bulb and spinal cord; a dopaminergic tract to the hypothalamus has been suggested (Mannisto et al., 1981) but there seems little evidence for such a projection.

GABA is a transmitter in the projections to the superior colliculus and the thalamus and some of these are collaterals (Bentivoglio et al., 1979; Anderson and Yoshida, 1980). GABA is also contained in the projections to the tegmentum and one group has estimated from physiological studies that some 40% of nigral neurons send inhibitory fibers to the tegmentum with about half of these having collaterals to either the thalamus and/or the superior colliculus (Niijima and Yoshida, 1982; Beckstead and Frankfurter, 1982). Collaterals within the SN of these projection neurons have also been suggested (Grofova and Fonnum, 1982) (see also references given for Figure 5).

Table 3: Some peptide neurotransmitter abnormalities reported in Parkinsonism and Huntington's Disease

	Huntington's			Parkinsonism	
Peptide	**CP**	**GP**	**SN**	**GP**	**SN**
Choleocystokinin	N[4]	D[4]	D[4]		D[7]
Neurotensin	I[1]				
Somatostatin*	I[1,3]	I[3]			
VIP	N[2]	N[2]			
Substance P	D[3]	D[3]		D[8]	D[8]
TRH	I[1,5]				
Vasopression #			N[6]		N[6]

N, normal; I, increased; D, decreased.

* The increase in somatostatin in the CP in Huntington's disease apparently reflects an increase in the varicose fibers rather than in cells (Marshall et al., 1982).

#CSF levels of vasopressin are reported decreased in Parkinsonism and dementia (Sundquist et al., 1983).

1) Nemeroff et al. (1983); 2) Emson et al. (1979); 3) Aronin et al. (1983); 4) Emson et al. (1980); 5) Spindel et al. (1980); 6) Rossor et al. (1982); 7) Studler et al. (1982); 8) Mauborgne et al. (1983).

Connections between Neurons

Even when the biochemical anatomy of tracts is defined, the circuitry is not known until the interconnections between these tracts have been established. Double labelling studies at the electron microscopic level are the only definitive means of establishing such connections and few such studies have been done. In the basal ganglia such work has indicated that dopamine innervates cholinergic neurons in the CP (Hattori et al., 1976) and that the many various types of striatal neurons destroyed by intrastriatal injections of kainic acid are innervated by afferents (presumably glutamatergic) from the cortex (Hattori et al., 1979). Light microscopic, pharmacological and binding studies can give some indication of interconnections but are not definitive. The pharmacological evidence that the dynorphin and substance P projections from the CP innervate neurons of the SNR (Proceddu et al., 1983) is in keeping with electron microscopic evidence involving double labeling (Hattori et al., 1975). A complete review of such studies is beyond the scope of this paper but much more work needs to be done on interconnections in the basal ganglia.

Conclusions

Some clues as to the roles of a few neurotransmitter systems in the functioning of the basal ganglia has been gained from a study of abnormalities in Huntington's disease and Parkinsonism. It is difficult, however, to fit the peptide abnormalities which have been reported (Table 3) into any rational scheme and changes in these, probably modulatory, systems may be secondary.

Having emphasized in this review the multiplicity of pathways and neurotransmitters in the basal ganglia, we would like now to focus on a relatively few (Figure 8). In this scheme, which borrows a great deal from Nauta (1979b), action in the basal ganglia is initiated when a "command" for movement comes from the cortex via the excitatory glutamate pathway. The dopamine input to the CP is a "hormonal" one and merely provides a continual damping of "static" so that the precise topography of the excitatory command can be appreciated. The inputs from the thalamus and many other regions are seen as being primarily a means of keeping the CP continually informed on the status of all the systems involved in movement. The CP has an integrator role and feeds its results via both excitatory and inhibitory pathways to the SNR/GP where they are translated into excitation or inhibition of GABA pathways which carry the detailed orders allowing the desired movement. In this scheme the connections of the SNR become of paramount importance. In a number of laboratories it has been shown that injection of various GABA or glycine antagonists into the nigra produce turning behaviour even in animals where the connections to the striatum have been severed (e.g. Andrews and Woodruff, 1982; Papadopoulos and Huston, 1980). Motamedi and York (1980) provided physiological evidence that the SNR to tegmental and tectal projections influence cervical cord spinal interneurons and may mediate the head turning behaviour seen after basal ganglia activation.

Although much of the literature has been focused on the nigrotectal projection, that to the tegmental area may be particularly important. This region is richly connected with other components of the extrapyramidal system. It receives afferents from the ipsilateral and possibly contralateral EP (Nauta, 1979a; Moon-Edley and Graybiel, 1980; Larsen and McBride, 1979) via collaterals of the entopedunculothalamic pathway which arises from the "motor" portion of the EP (van der Kooy and Carter, 1981). A reciprocal relation with the subthalamic nucleus has been suggested (Jackson and Crossman, 1981a). Additional inputs to this tegmental area include those from the amygdala, hypothalamus and ventrocaudal regions of the CP and GP (Jackson and Crossman, 1981b). Efferent projections from the pedunculopontine nucleus have been described to all of the areas from which it receives afferents

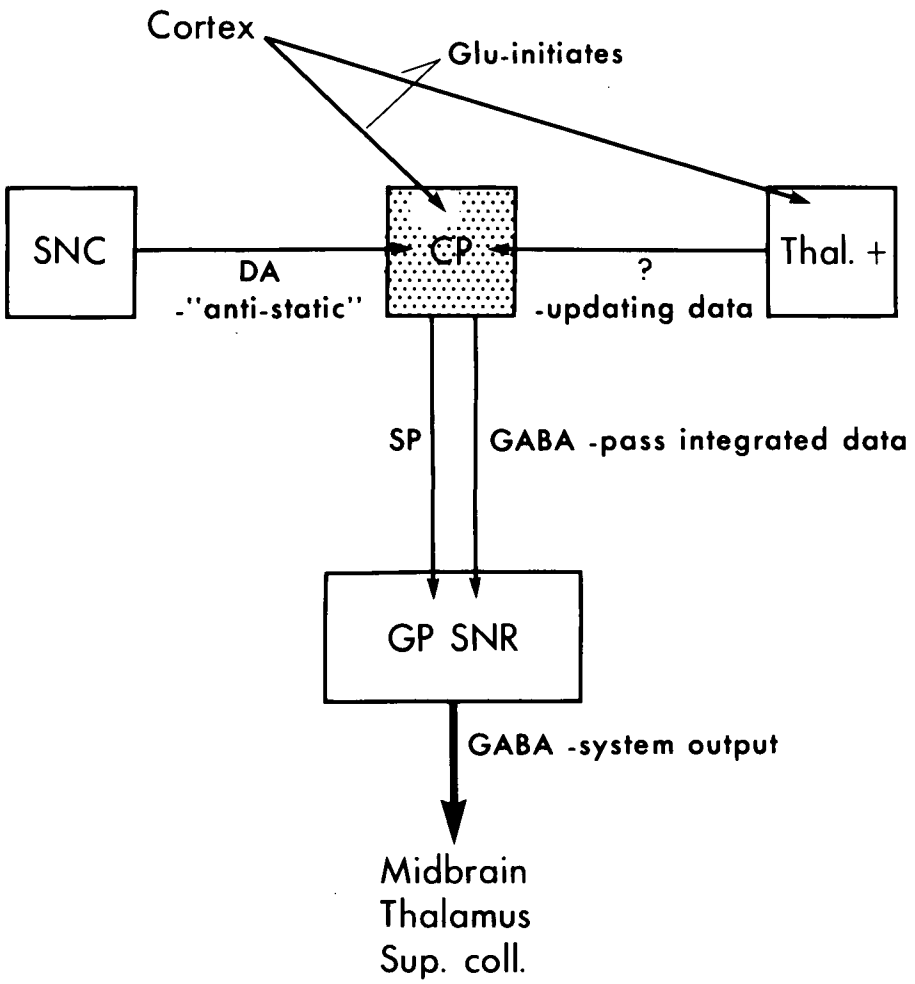

Figure 8 — A hypothetical diagram of information flow in the basal ganglia. Thal+ stands for all regions projecting to the CP except the cortex and SNC.

(Tohyama et al., 1978; Moon-Edley and Graybiel, 1980; Saper and Loewy, 1982). Some of the widespread connections presently attributed to this nucleus may, in fact, arise from the nucleus parabrachialis, a cholinergic cell group (Kimura et al., 1981, 1984) surrounding the brachium conjunctivum and probably sending diffuse projections both rostrally and caudally.

A point of possible interest is the high degree of convergence of SNR and cerebellar projections. Common target areas include the superior colliculus, dorsal midbrain tegmentum, and the parafascicular and ventromedial nuclei of the thalamus. These overlapping inputs may allow for the coordination of basal ganglia and cerebellar influences on motor control.

It is even possible that some movement disorders, such as torticollis, may arise from a failure to develop or maintain the bilateral connections which presumably provide for integration. And the SNR is clearly involved in many of these bilateral connections. It may, therefore, be this small nucleus which plays a pivotal role in the functioning of the basal ganglia.

References

Anderson ME, Yoshida M (1980) Axonal branching patterns and location of nigrothalamic and nigrocollicular neurons in the cat. J. Neurophysiol. 43: 883-895.

Andrews CD, Woodruff GN (1982) Turning behaviour following nigral injections of dopamine agonists and glycine. Eur. J. Pharmacol. 84: 169-175.

Araki M, McGeer PL, McGeer EG (1984a) Presumptive GABAergic pathways from the midbrain to the superior colliculus studied by a combined HRP-GABA transaminase pharmacohistochemical method. Neuroscience, in press.

Araki M, McGeer PL, McGeer EG (1984b) Retrograde HRP tracing combined with a pharmacohistochemical method for GABA transaminase for the identification of presumptive GABAergic projections to the habenula. Brain Res., in press.

Arbuthnott GW, Walker RH, Whale D, Wright AK (1982a) Further evidence for a pallidostriatal pathway in rat brain. Physiol. Soc. Abst. p. 33.

Arbuthnott GW, Wright AK, Hamilton MH, Brown JR (1982b) Orthograde transport of Nuclear yellow: a problem and its solution. J. Neurosci. Methods 6: 365-368.

Aronin N, Cooper PE, Lorenz LJ, Bird ED, Sagar SM, Leeman SE, Martin JB (1983) Somatostatin is increased in the basal ganglia in Huntington Disease. Ann. Neurol. 13: 519-526.

Barbin G, Garbarg M, Lorens-Cortes C, Palacios CM, Pollard H, Schwartz JC (1977) Biochemical mapping of histaminergic pathways and cell bodies in brain. Intl. Soc. Neurochem. Abstracts, 6: 443.

Beach TG, McGeer EG (1984) The distribution of Substance P in the primate basal ganglia: an immunohistochemical study of baboon and human brain. Neuroscience, in press.

Beal MF, Martin JB (1983) Effects of lesions on somatostatin-like immunoreactivity in the rat striatum. Brain Res. 266: 67-73.

Beckstead RM (1979) Convergent prefrontal and nigral projections to the striatum of the rat. Neurosci. Lett. 12: 59-64.

Beckstead, RM (1983) A reciprocal axonal connection between the subthalamic nucleus and the neostriatum in the cat. Brain Res. 275: 137-142.

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Beckstead RM, Frankfurter A (1982) The distribution and some morphological features of substantia nigra neurons that project to the thalamus, superior colliculus and pedunculopontine nucleus in the monkey. Neuroscience 7: 2377-2388.

Beitz AJ (1982) The sites of origin of brain stem neurotensin and serotonin projections to the rodent nucleus raphe magnus. J. Neurosci. 7: 829-842.

Bentivoglio M, Van der Kooy D, Kuypers HGJM (1979) The organization of the efferent projections of the substantia nigra in the rat. A retrograde fluorescent double labelling study. Brain Res. 174: 1-17.

Bolam JP, Powell JF, Totterdell S, Smith AD (1981) The proportion of neurons in the rat neostriatum that project to the substantia nigra demonstrated using horseradish peroxidase conjugated with wheat germ agglutinin. Brain Res. 220: 339-343.

Brann MR, Emson PC (1980) Microiontophoretic injection of fluorescent tracer combined with simultaneous immunofluorescent histochemistry for the demonstration of efferents from the caudate putamen projecting to the globus pallidus. Neurosci. Lett. 16: 61-66.

Brown LL, Makman MH, Wolfson LI, Dvorkin B, Warner C, Katzman R (1979) A direct role of dopamine in the rat subthalamic nucleus and adjacent intrapeduncular area. Science 206: 1416-1418.

Brownstein MJ, Mroz EH, Tappaz NL, Leeman SE (1977) On the origin of substance P and glutamic acid decarboxylase (GAD) in the substantia nigra. Brain Res. 135: 315-323.

Buchwald NA, Fisher RS, Levine MS, Gazarra R, Hull CD (1981) Connectivity of the caudate nucleus in newborn kittens and adult cats. Soc. Neurosci. Abstr. 7: 192.

Carter DA, Fibiger HC (1978) The projections of the entopeduncular nucleus and globus pallidus in rat as demonstrated by autoradiography and horseradish peroxidase histochemistry. J. Comp. Neurol. 177: 113-124.

Chang HT, Wilson CJ, Kitai ST (1981) Single neostriatal efferent axons in the globus pallidus: a light and electron microscopic study. Science 2: 915-917.

Chesselet MF, Reisine TC, Glowinski J, Graybiel AM (1982) Striatal somatostatin: immunohistochemistry and effects on dopaminergic transmission. Soc. Neurosci. Absts. 8: 287.

Chevalier G, Deniau JM, Thierry AM, Feger J (1981a) The nigrotectal pathway. An electrophysiological reinvestigation in the rat. Brain. Res. 213: 253-263.

Chevalier G, Thierry AM, Shibazaki T, Feger J (1981b) Evidence for a GABAergic inhibitory nigrotectal pathway in the rat. Neurosci. Lett. 21: 67-70.

Childs JA, Gale K (1983) Neurochemical evidence for a nigrotegmental GABAergic projection. Brain Res. 258: 109-114.

Chung YW, Hassler R (1982) Anterograde and retrograde degenerative reactions in caudate nucleus and putamen after experimental lesion of the pallidum in squirrel monkey (Saimiri ciureas). Acta Anat. 13: 246-263.

Clavier RM, Atmadja S, Fibiger HC (1976) Nigrothalamic projections in the rat as demonstrated by orthograde and retrograde tracing techniques. Brain Res. Bull. 1: 379-384.

Collingridge GL, Davies J (1981) The influence of striatal stimulation and putative neurotransmitters on identified neurons in the rat substantia nigra. Brain Res. 212: 345-359.

Connor JD (1975) Electrophysiology of the nigra-caudate dopamine pathway. Pharmac. Therap. B. 1: 357-370.

Contestabile A, Fonnum F (1983) Cholinergic and GABAergic forebrain projections to the habenula and nucleus interpeduncularis: surgical and kainic acid lesions. Brain Res. 275: 287-297.

Davies P, Josef J, Thompson A (1981) Anterior to posterior variations in the concentration of somatostatin-like immunoreactivity in human basal ganglia. Brain Res. Bull. 7: 365-368.

De Bellefeuille L, Parent A (1982) Fluorescent retrograde study of the pallidointralaminar and pallidonigral pathways in primate. Neurosci. Abst. 8: 169.

Del Fiacco M, Paxinos G, Cuello AC (1982) Neostriatal enkephalin-immunoreactive neurons project to the globus pallidus. Brain Res. 231: 1-17.

Deniau JM, Hammond C, Chevalier G, Feyer J (1978a) Evidence for branched subthalamic nucleus projections to substantia nigra, entopeduncular nucleus and globus pallidus. Neurosci. Lett. 9: 117-121.

Deniau JM, Hammond C, Riszk A, Feyer J (1978b) Electrophysiological properties of identified output neurons of the substantia nigra (pars compacta and pars reticulata): evidence for the existence of branched neurons. Exp. Brain Res. 32: 409-422.

de Quidt ME, Emson PE (1983) Neurotensin facilitates dopamine release in vitro from rat striatal slices. Brain Res. 274: 376-380.

DiFiglia M, Aronin N (1982) Ultrastructural features of immunoreactive somatostatin neurons in the rat caudate nucleus. J. Neurosci. 2: 1267-1274.

DiFiglia M, Pasik T, Pasik P (1978) A Golgi study of afferent fiber in the neostriatum of monkeys. Brain Res. 152: 341-347.

Donoghue JP, Kitai ST (1981) A collateral pathway to the neostriatum from corticofugal neuron of the rat sensory motor cortex. An intracellular HRP study. J. Comp. Neurol. 201: 1-13.

Dray A (1979) The striatum and substantia nigra: A commentary on their relationship. Neuroscience 4: 1407-1439.

Edstrom JP, Phillis JW (1980) A cholinergic projection from the globus pallidus to the cerebral cortex. Brain Res. 189: 524-529.

Emson PD, Fahrenkrug J, Spokes EGS (1979) Vasoactive intestinal peptide (VIP): distribution in normal human brain and in Huntington's disease. Brain Res. 173: 174-178.

Emson PC, Rehfeld JHF, Langevin H, Rossor M (1980) Reduction in choleocystokinin-like immunoreactivity in the basal ganglia in Huntington's disease. Brain Res. 198: 496-500.

Emson PC, Goedert M, Horsfield P, Rioux F, St. Pierre S (1982) The regional distribution and chromatographic characterization of neurotensin-immunoreactivity in the rat central nervous system. J. Neurochem. 38: 992-999.

Fallon JH, Ziegler BTS (1979) The crossed cortico-caudate projection in the rhesus monkey. Neurosci. Lett. 15: 29-32.

Fibiger HC, Pudritz RE, McGeer PL, McGeer EG (1972) Axonal transport in nigro-striatal and nigro-thalamic neurons; effects of medial forebrain bundle lesions and 6-hydroxydopamine. J. Neurochem. 19: 1697-1708.

Finley JCW, Grossman GH, Dimeo P, Petrusz P (1978) Somatostatin containing neurons in the rat brain: widestread distribution revealed by immunocytochemistry after pretreatment with pronase. Amer. J. Anat. 153: 483-488.

Gerfen CR, Staines WA, Arbuthnot GW, Fibiger HC (1982) Crossed connections of the substantia nigra in the rat. J. Comp. Neurol. 207: 283-303.

Goedert M, Emson PC (1983) The regional distribution of neurotensin-like immuoreactivity in central and peripheral tissues of the cat. Brain Res. 272: 291-297.

Goedert M, Manthy PW, Hunt SP, Emson PC (1983) Mosaic distribution of neurotensin-like immunoreactivity in the cat striatum. Brain Res. 274: 176-179.

Goodman RR, Huhar MJ, Hester L, Snyder SH (1983) Adenosine receptors: autoradiographic evidence for their location on axon terminals of excitatory neurons. Science 220: 967-8.

Graybiel AM, Ragsdale CWJr, Yoneoka ES, Elde RP (1981) An immunohistochemical study on enkephalins and other neuropeptides in the striatum of the cat with evidence that the opiate peptides are arranged to form mosaic patterns in register with the striosomal compartments visible by acetylcholinesterase staining. Neuroscience 6: 377-397.

Grofova I, Fonnum F (1982) Extrinsic and intrinsic origin of GAD in pars compacta of the rat substantia nigra. Soc. Neurosci. Abst. 8: 961.

Haber S, Elde R (1981) Correlation between met-enkephalin and substance P immunoreactivity in the primate globus pallidus. Neuroscience 6: 1291-1297.

Hattori T, Fibiger HC, McGeer PL (1975) Demonstration of a pallidonigral projection innervating dopaminergic neurons. J. Comp. Neurol. 162: 487-504.

Hattori T, Singh VK, McGeer EG, McGeer PL (1976) Immunohistochemical localization of choline acetyltransferase-containing neostriatal neurons and their relationship with dopaminergic synapses. Brain Res. 102: 164-173.

Hattori T, McGeer EG, McGeer PL (1979) Fine structural analysis of the cortico-striatal pathway. J. Comp. Neurol. 185: 347-353.

Hedreen J (1977) Corticostriatal cells identified by the peroxidase method. Neurosci. Lett. 4: 1-7.

Hedreen J (1978) Nondopaminergic and dopaminergic nigrostriatal pathways in rats. Soc. Neurosci. Absts. 4: 45.
Herkenham M (1979) The afferent and efferent connections of the ventromedial thalamic nucleus in the rat. J. Comp. Neurol. 183: 487-518.
Jackson A, Crossman AR (1981a) Subthalamic projection to nucleus tegmenti pedunculopontinus in the rat. Neurosci. Lett. 22: 17-22.
Jackson A, Crossman AR (1981b) Basal ganglia and other afferent projections to the peribrachial region in the rat. A study using retrograde and anterograde transport of horseradish peroxidase. Neuroscience 6: 1537-1549.
Jayaraman A (1983) Topographic organization and morphology of peripallidal and pallidal cells projecting to the striatum in cats. Brain Res. 275: 279-286.
Jennes L, Stumpf WE, Kalivas PW (1982) Neurotensin: topographical distribution in rat brain by immunohistochemistry. J. Comp. Neurol. 210: 211-224.
Jessel TM, Emson PC, Paxinos G, Cuello AC (1978) Topographic projections of substance P and GABA pathways in the striato- and pallidonigral system: a biochemical and immunohistochemical study. Brain Res. 152: 487-498.
Jones EG, Leavitt RY (1975) Retrograde axonal transport and the demonstration of nonspecific projections to the cerebral cortex and striatum from thalamic intralaminar nuclei in the rat, cat and monkey. J. Comp. Neurol. 154: 349-378.
Kelley AE, Domestick VB, Nauta WJH (1982) The amygdalostriatal projection in the rat — an anatomical study by anterograde and retrograde tracing methods. Neuroscience 7: 615-630.
Kelly PH, Moore KE (1980) Decrease of cortical choline acetyltransferase after lesion of the globus pallidus in the rat. Exp. Neurol. 61: 479-484.
Kim R, Nakano K, Hayaramon A, Carpenter MB (1976) Projections of the globus pallidus and adjacent structures: An autoradiographic study in the monkey. J. Comp. Neurol. 169: 263-290.
Kimura H, McGeer PL, Peng JH, McGeer EG (1981) The central cholinergic system studied by choline acetyltransferase immunohistochemistry in the cat. J. Comp. Neurol. 200: 151-201.
Kimura H, Peng JH, McGeer PL (in press). Choline acetyltransferse containing neurons in rat brain. *In*: A. Bjorklund and T. Hokfelt (eds.), Handbook of Chemical Neuroanatomy, Elsevier Press, The Netherlands.
Larsen KD, McBride RL (1979) The organization of feline entopeduncular nucleus projections. Anatomical Studies. J. Comp. Neurol. 184: 293-308.
Leichnetz GR (1981) The median subcallosal fasciculus in the monkey: A unique prefrontal corticostriate and corticocortical pathway revealed by anterogradely transported horseradish peroxidase. Neurosci. Lett. 21: 137-142.
Loughlin SE, Fallon JH (1982) Mesostriatal projections from ventral tegmentum and dorsal raphe cells project ipsilaterally or contralaterally but not bilaterally. Neurosci. Lett. 32: 11-16.
McGeer EG, McGeer PL, Vincent SR (1982) GABA enzymes and pathways. *In*: H.F. Bradford (ed), Neurotransmitter Interaction and Compartmentation, Nato Advanced Study Institutes Series A, Vol. 48, Plenum Press, New York and London pp. 299-327.
McGeer PL, McGeer EG (1981) Amino acid neurotransmitters. *In*: G.J. Siegel, R.W. Albers, B.W. Agranoff and R. Katzman (eds.), Basic Neurochemistry, Little, Brown and Co., Boston pp. 233-254.
McGeer PL, McGeer EG, Scherer U, Singh K (1977) A glutamatergic corticostriatal path? Brain Res. 128: 369-373.
McGeer PL, Kimura H, McGeer EG, Peng JH (1982) Cholinergic systems in the CNS. *In*: H.F. Bradford (ed), Neurotransmitter Interaction and Compartmentation, Nato Advanced Study Institutes Series A, Vol. 48, Plenum Press, New York and London pp. 253-289.
McGeer PL, McGeer EG, Nagai T (1983) GABAergic and cholinergic indices in various regions of rat brain after intracerebral injections of folic acid. Brain Res. 260: 107-116.
Manberg PJ, Youngblood WW, Nemeroff CB, Rossor MN, Iversen LL, Prange AJ Jr, Kizer JS (1982) Regional distribution of neurotension in human brain. J. Neurochem. 38: 1777-1780.
Mannisto P, Mattila J, Kaakkola S (1981) Possible involvement of nigrostriatal dopamine system in the inhibition of thyrotropin secretion in the rat. Eur. J. Pharmacol. 76: 403-409.
Marshall PE, Burd GD, Landis DMD (1982) Somatostatin in the neostriatum and substantia nigra in normal human brain and in Huntington's disease. Soc. Neurosci. Abst. 8: 507.
Mauborgne A, Javoy-Agid F, Legrand JC, Agid Y, Cesselin F (1983) Decrease of substance P-like immunoreactivity in the substantia nigra and pallidum of parkinsonian brains. Brain Res. 268: 167-170.
Matsuzaki T, Shiosaka S, Inagaki S, Sakanaka M, Takatsuki K, Takagi H, Senba E, Kawai Y, Tohyama M (1981) Distribution of neuropeptides in the dorsal pontine tegmental area of the rat. Cell. & Mol. Biol. 27: 499-508.
Meibach RC, Katzman R (1981) Origin, course and termination of dopaminergic substantia nigra neurons projecting to the amygdaloid complex in the cat. Neuroscience 6: 2159-2171.
Meyer DK, Beinfeld MC, Oertel WH, Brownstein MJ (1982) Origin of the choleocystokinin-containing fibers in the caudatoputamen. Science 215: 187-8.
Moon-Edley, Graybiel A, (1980) Connections of the nucleus tegmenti pedunculopontinus pars compacta TPc in cat. Anat. Rec. 195: 128a.
Motamedi F, York DH (1980) Effects of a nigral descending pathway on cervical spinal cord afferent fibers and interneurons. Exp. Neurol. 68: 258-268.
Nagai T, McGeer PL, McGeer EG (1983) Distribution of GABA-T-intensive neurons in the rat forebrain and midbrain. J. Comp. Neurol. 218: 220-238.
Nakano K, Kohno M, Kawahira J, Tokushige A (1982) Entopeduncular nucleus projections to the contralateral thalamic nuclei: an HRP study. Brain Res. 262: 283-287.
Nauta HJW (1979a) Projections of the pallidal complex: An autoradiographic study in the cat. Neuroscience 4: 1853-1873.
Nauta HJW (1979b) A proposed conceptual reorganization of the basal ganglia and telencephalon. Neuroscience 4: 1875-1881.
Nauta, HJW, Cole M (1978) Efferent projections of the subthalamic nucleus: An autoradiographic study in the monkey and cat. J. Comp. Neurol. 180: 1-16.
Nemeroff CB, Youngblood WW, Manberg PJ, Prange AJ Jr., Kizer JS (1983) Regional brain concentrations of neuropeptides in Huntington's chorea and schizophrenia. Science 221: 972-974.
Nijima K, Yoshida M (1982) Electrophysiological evidence for branching nigral projections to pontine reticular formation, superior colliculus and thalamus. Brain Res. 239: 279-282.
Nilaver G, Hoffman DL, Zimmerman EA (1979) Multiple projections of the magnocellular hypothalamus to other brain regions including cerebral cortex. Trans. Am. Neurol. Assoc. 104: 205-208.
Oka (1980) Organization of the cortico-caudate projections. A horseradish peroxidase study in the cat. Exp. Brain Res. 40: 203-208.
Palacios JM, Kuhar MJ (1981) Neurotensin receptors are located on dopamine-containing neurons in rat midbrain. Nature 294: 587-589.
Papadopoulos G, Huston JP (1980) Removal of the telencephalon spares tuning induced by injection of GABA agonists and antagonists into the substantia nigra. Behav. Brain Res. 1: 25-38.
Park MR, Falls WM, Kitai ST (1982) An intracellular HRP study of the rat globus pallidus. I. Responses and light microscopic analysis. J. Comp. Neurol. 211: 284-294.
Pinnock RD, Dray A (1982) Differential sensitivity of presumed dopaminergic and non-dopaminergic neurons in rat substantia nigra to electrophoretically applied substance P. Neurosci. Lett. 29: 153-158.
Pollard H, Lores-Cortes C, Barbin G, Garbarg M, Schwartz JC (1978) Histamine and histidine decarboxylase in brain stem nuclei: distribution and decrease after lesions. Brain Res. 157: 178-181.
Porceddu ML, Imperato A, Melis MR, Di Chiara G (1983) Role of ventral mesencephalic reticular formation and related noradrenergic and serotonergic bundles in turning behaviour as investigated by means of kainate, 6-hydroxydopamine and 5,7-dihydroxytryptamine lesions. Brain Res. 261: 187-200.
Ribak CE, Kramer WG (1982) Cholinergic neurons in the basal forebrain of the cat have direct projections to the sensorimotor cortex. Exp. Neurol. 75: 453-465.
Ricardo JA (1980) Efferent connections of the subthalamic region in the rat. I. the subthalamic nucleus of Luys. Brain Res. 202: 257-271.
Ricciardi G, Forchetti C, Gasbarri A, Scarnati E, Pacitti C (1981) Proprieta a'neuroeccitatorie dell'acido kainico. II) Danni neuronali susseguenti a microiniezioni intracerebrali in ratti, Boll. Soc. Ital. Biol. Sper. 57: 919-925.

Rossor MN, Hunt SP, Iversen LL, Bannister R, Hawthorn J, Ang VTY, Jenkins JS (1982) Extrahypothalamic vaspressin is unchanged in Parkinson's disease and Huntington's disease. Brain Res. 253: 341-343.

Royce GJ (1978) Cells of origin of subcortical afferents to the caudate nucleus: A horseradish peroxidase study in the cat. Brain Res. 153: 465-475.

Royce GJ (1982) Laminar origin of cortical neurons which project upon the caudate nucleus: A horseradish peroxidase investigation in the cat. J. Comp. Neurol. 205: 8-29.

Rouzaire-Dubois B, Scarnati E, Hammond C, Crossman AR, Shibazaki, T (1983) Microiontophoretic studies on the nature of the neurotransmitter in the subthalamo-entopeduncular pathway of the rat. Brain Res. 271: 11-20.

Sakanaka M, Shiosaka S, Takatsuki K, Tohyama M (1983) Evidence for the existence of a substance P-containing pathway from the nucleus laterodorsalis tegmenti (Castaldi) to the medial frontal cortex of the rat. Brain Res. 259: 123-126.

Saper CB, Loewy AD (1982) Projections of the pedunculopontine tegmental nucleus in the rat: evidence for additional extrapyramidal circuitry. Brain Res. 252: 367-372.

Scarnati E, Campara E, Pacitti C (1983) The functional role of the nucleus accumbens in the control of the substantia nigra: Electrophysiological investigations in intact and striatum-globus pallidus lesioned rats. Brain Res. 265: 249-257.

Scatton B, Worms P, Lloyd KG, Bartholini G (1982) Cortical modulation of striatal function. Brain Res. 232: 331-343.

Smith AD, Bolam JP, Somogyi (1981) An approach to the identification of neurotransmitters in characterized synapses of complex neuronal networks: application to the basal ganglia of the rat. *In*: Chemical Neurotransmission 75 years, L. Stjarne, P. Hedqvist, H. Lagercrantz and A. Wennmalm (Eds.), Academic Press, New York pp. 463-479.

Sofroniew MV (1980) Projections from vasopressin, oxytocin, and neurophysin neurons to neural targets in the rat and human. J. Histochem. Cytochem. 28: 475-478.

Somogyi P, Priestley JV, Cuello AC, Smith AD, Takagi H (1982) Synaptic connections of enkephalin-immunoreactive nerve terminals in the neostriatum: a correlated light and electron microscopic study. J. Neurocytol. 11: 779-807.

Spindel ER, Wurtman RJ, Bird ED (1980) Increased TRH content of the basal ganglia in Huntington's disease. N. Engl. J. Med. 303: 1235-1236.

Spindel ER, Pettibone DJ, Wurtman RHJ (1981) Thyrotropin-releasing hormone (TRH) content of rat striatum: modification by drugs and lesions. Brain Res. 216: 323-331.

Staines WA, Nagy JI, Vincent SR, Fibiger HC (1980) Neurotransmitters contained in the efferents of the striatum. Brain Res. 194: 391-402.

Staines WA, Atmadja S, Fibiger HC (1981) Demonstration of a pallidostriatal pathway by retrograde transport of HRP-labelled lectin. Brain Res. 206: 446-450.

Starr MS, Kilpatrick IC (1981) Distribution of GABA in the rat thalamus; specific decrease in thalamic GABA following lesion or electrical stimulation of the substantia nigra. Neuroscience 6: 1095-1104.

Studler JM, Javoy-Agid F, Cesselin F, Legrand JC, Agid Y (1982) CCK-8-Immunoreactivity distribution in human brain: selective decrease in the substantia nigra of parkinsonian patients. Brain Res. 243: 176-179.

Sugimoto T, Hattori T (1983) Confirmation of thalamosubthalamic projections by electron microscopic autoradiography. Brain Res. 267: 335-339.

Sugimoto TO, Mizuno N, Itoh K (1981) An autoradiographic study on the terminal distribution of cerebellothalamic fibers in the cat. Brain Res. 215: 29-47.

Sundquist J, Forsling ML, Olsson JE, Akerlund M (1983) Cerebrospinal fluid arginine vasopressin in degenerative disorders and other neurological diseases. J. Neurol. Neurosurg. Psychiatry 46: 14-17.

Takatsuki K, Shinosaka S, Sakanaka M, Inagaki S, Semba E, Takagi H, Tohyama M (1981) Somatostatin in the auditory system of the rat. Brain Res. 213: 211-216.

Tohyama MK, Satoh K, Sakumoto T, Kimoto Y, Takahashi Y, Yamamoto K, Itakura T (1978) Organization and projections of the neurons in the dorsal tegmental area of the rat. J. Hirnforsch. 19: 165-176.

Tulloch IF, Arbuthnott GW, Wright AK (1978) Topographical organization of the striatonigral pathway revealed by anterograde and retrograde neuroanatomical tracing techniques. J. Anat. 127: 425-441.

Ueki A (1983) The mode of nigro-thalamic transmission investigated with intracellular recording in the cat. Exp. Br. Res. 49: 116-124.

Uhl GR, Goodman RR, Snyder SH (1979) Neurotensin-containing cell bodies, fibers and nerve terminals in the brain stem of the rat: immunohistochemical mapping. Brain Res. 1667: 77-91.

Uhl GR, Snyder SH (1976) Regional and subcellular distributions of brain neurotensin. Life Sci. 19: 1827-1832.

van der Kooy D (1979) The organization of the thalamic, nigral and raphe cells projecting to the medial vs. lateral caudate putamen in rat. A fluorescent retrograde double labelling study. Brain Res. 169: 382-387.

van der Kooy D, Carter D (1981) The organization of the efferent projections and striatal afferents of the entopeduncular and adjacent areas in the rat. Brain Res. 211: 15-36.

van der Kooy D, Hattori T (1980) Single subthalamic nucleus neurons project to both the globus pallidus and substantia nigra in rat. J. Comp. Neurol. 192: 751-768.

van der Kooy D, Coscina DV, Hattori T (1981) Is there a non-dopaminergic nigrostriatal pathway? Neuroscience 6: 345-357.

Veening GJ, Cornelissen FM, Lieven PAJM (1980) The topical organization of the efferents to the caudatoputamen of the rat. A horseradish peroxidase study. Neuroscience 5: 1253-1268.

Vincent SR, Hokfelt T, Christensson I, Terenius L (1982a) Dynorphin-immunoreactive neurons in the central nervous system of the rat. Neurosci. Lett. 33: 185-190.

Vincent SR, Hokfelt T, Christensson I, Terenius L (1928b) Immunohistochemical evidence for a dynorphin immunoreactive striatonigral pathway. Eur. J. Pharmacol. 85: 251-252.

Vincent SR, Skirboll L, Hokfelt T, Johansson O, Lundberg JM, Elde RP, Terenius L, Kimmel J (1982c) Coexistence of somatostatin and avian pancreatic polypeptide (APP)-like immunoreactivity in some forebrain neurons. Neuroscience 7: 439-446.

Vincent SR, Staines WA, Fibiger HC (1983a) Histochemical demonstration of separate populations of somatostatin and cholinergic neurons in the rat striatum. Neurosci. Lett. 325: 111-114.

Vincent SR, Hokfelt T, Skirboll L, Wu, J.-Y (1983b) Hypothalamic γ-aminobutyric acid neurons project to the neocortex. Science 220: 1309-1310.

Walker JE (1983) Glutamate, GABA, and CNS disease: A review. Neurochem. Res. 8: 521-550.

Wojcik WJ, Neff NH (1983) Adenosine A1 receptors are associated with cerebellar granule cells. J. Neurochem. 41: 759-763.

Wilson CJ, Phelan KD (1982) Dual topographic representation of neostriatum in the globus pallidus of the rat. Brain Res. 243: 354-359.

Yang, HYT, Panula, P, Tang J, Costa E (1983) Characterization and localization of Met^5-enkephalin-Arg^6-Phe^7 stored in various rat brain regions. J. Neurochem. 40: 969-976.

Yeterian EH, van Hoesen GW (1978) Corticostriate projection in the monkey: The organization of certain corticostriate connections. Brain Res. 139: 43-63.