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Excitatory amino acidergic pathways and receptors in the basal ganglia

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Summary. The striatum receives the majority of excitatory amino acidergic input to the basal ganglia from neocortical and allocortical sources. The subthalamic nucleus and the substantia nigra also receive excitatory amino acidergic inputs from neocortex. The subthalamic nucleus, which has prominent projections to the pallidum and nigra, is the only known intrinsic excitatory amino acidergic component of the basal ganglia. Possible excitatory amino acidergic inputs reach the basal ganglia from the intralaminar thalamic nuclei and the pedunculopontine nucleus. The striatum is richly endowed with all subtypes of excitatory amino acid receptors and these appear to be inhomogeneously distributed within the striatal complex. The non-striatal nuclei contain lesser levels of excitatory amino acid receptors and the relative proportion of these receptors varies between nuclei. The presence of high densities of excitatory amino acid receptors is a phylogenetically conserved feature of the striatum and its non-mammalian homologues. In Huntington's disease, there is substantial depletion of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, N-methyl-D-aspartate, and kainate receptors within the striatum. In Parkinson's disease substantia nigra, there is significant loss of N-methyl-D-aspartate and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors.

Keywords: Amino acids – Glutamate – Aspartate – α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid – Kainate – N-Methyl-D-asparate – Striatum – Pallidum – Substantia nigra – Subthalamic nucleus

Introduction

Excitatory amino acids (EAAs) are the predominant excitatory neurotransmitter(s) within the central nervous system. Their function(s) have, therefore, become a central issue in contemporary neurobiology. While considerable research has focused on such cytoarchitectonically simple regions as the hippocampus, the cerebellum, and the spinal cord, the role of EAAs in more complex regions of the neocortex and basal ganglia is now being explored. In this article

we review the organization of EAAergic pathways involving the basal ganglia, the distribution of EAA binding sites within the basal ganglia, the comparative anatomy of EAA binding site distribution within the striatopallidal complex, and changes in EAA binding sites in human basal ganglia diseases.

EAAergic pathways involving the basal ganglia

The best characterized EAAergic pathway involving the basal ganglia is the massive neocorticostriate projection (Fig. 1). Data from biochemical (Fonnum et al., 1981; Girault et al., 1986; Godukhin et al., 1980; Hassler et al., 1982; McGeer et al., 1977), electrophysiological (Herrling, 1985; Spencer, 1976; Stone, 1979), immunocytochemical (Dinopoulos et al., 1989), and [^{3}H]D-aspartate tracing studies (Streit, 1980) leads to the conclusion that EAAs are the primary neurotransmitter of neocorticostriate neurons. The anatomy of this projection appears to be complex. While it is clear that the neocorticostriate projection has a topographic character (Kemp and Powell, 1970; McGeorge and Faull, 1989), it is now known that cortical projections to the so-called 'patch' and 'matrix' components of the striatum differ in terms of regional and laminar origin (Donoghue and Herkenham, 1986; Gerfen, 1989). Most studies of neocorticostriate projection anatomy have been done in rat brain and there are indications that the organization of neocorticostriate projections is more complicated in animals with more differentiated cortices (Tanaka, 1987; Selemon and Rakic, 1985).

Just as the striatum proper receives massive EAAergic innervation from the neocortex, the ventral portions of the striatal complex, the nucleus accumbens and olfactory tubercule, receive innervation from neocortical regions but also from limbic, allocortical regions including the subiculum of the hippocampal formation, the basolateral nucleus of the amygdala, and the primary olfactory cortex (Fig. 1) (McGeorge and Faull, 1989). While studies directed at identifying the neurotransmitter of these allocortical striatal afferents are limited, the available evidence indicates that EAAs are the primary neurotransmitters of these pathways (Robinson and Beart, 1988; Christie et al., 1985a; Walaas, 1981; Walaas and Fonnum, 1979; Fuller et al., 1987).

Two other basal ganglia nuclei receive neocortical input (Fig. 1). The subthalamic nucleus is the target of a well characterized projection from frontal cortex (Afsharpour, 1985). Afsharpour (1985) has suggested that subthalamic nucleus afferents from the neocortex may be collaterals of corticobulbar and corticospinal neurons. Electrophysiological evidence indicates that this projection is EAAergic and acts through non-N-methyl-D-aspartate receptors (Rouzaire-Dubois and Scarnati, 1987b; Rouzaire-Dubois and Scarnati, 1987a). The substantia nigra also receives afferents from neocortex. Both retrograde and anterograde tracing studies indicate the presence of a neocortico-nigral pathway that appears to terminate mainly on dopaminergic neurons (Beckstead, 1979; Bunney and Aghajanian, 1976), and biochemical evidence suggests that this pathway is EAAergic (Kornhuber et al., 1985; Christie et al., 1985b).

The only intrinsic portion of the basal ganglia that uses EAAs as a neurotransmitter is the subthalamic nucleus (STN). While the STN was thought for

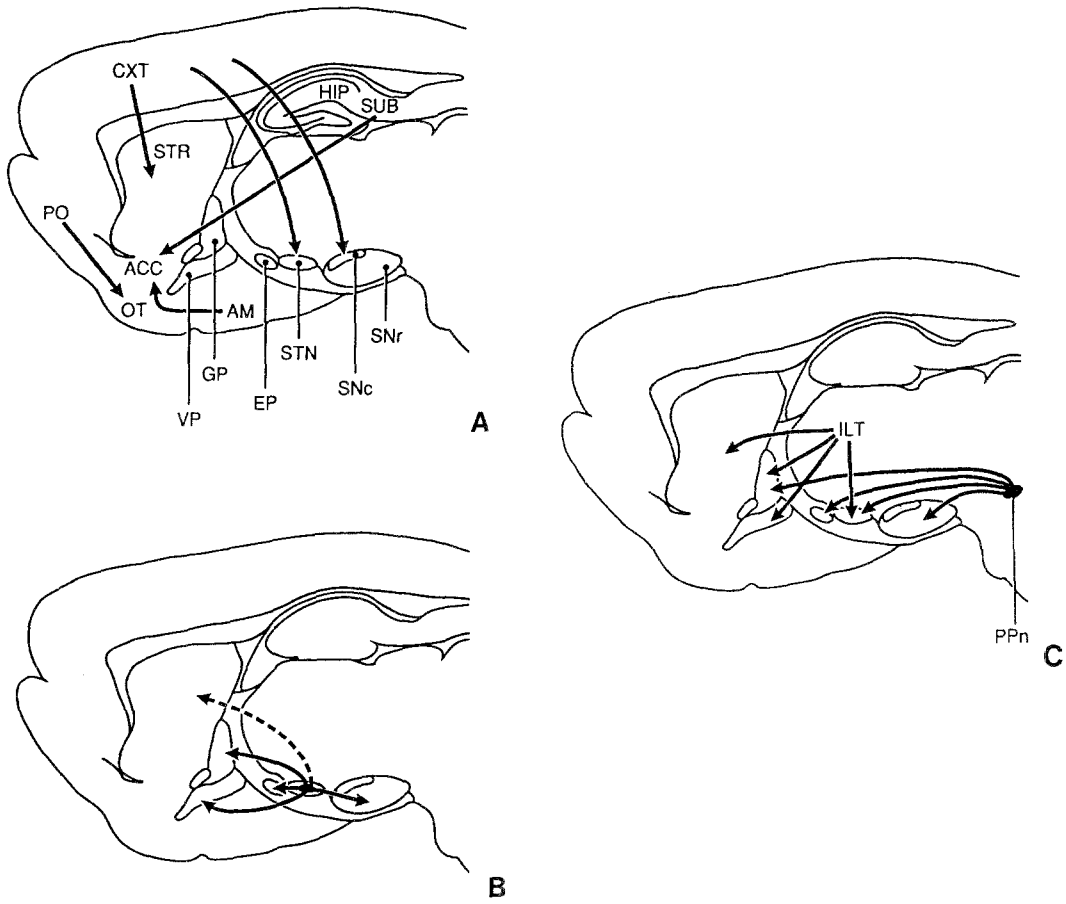

Fig. 1. Excitatory amino acidergic pathways involving the basal ganglia of the rat. (**A**) Confirmed excitatory amino acidergic afferents of the basal ganglia. (**B**) Projections of the subthalamic nucleus. The striatal efferent is represented as a dashed line to indicate that it is a weak projection in rats but may be more substantial in other mammals. (**C**) Possible excitatory amino acidergic afferents to the basal ganglia. *CXT* neocortex, *PO* primary olfactory cortex, *HIP* hippocampus, *SUB* subiculum, *STR* dorsal striatum, *ACC* nucleus accumbens, *OT* olfactory tubercule, *GP* globus pallidus, *VP* ventral pallidum, *EP* entopeduncular nucleus, *STN* subthalamic nucleus, *SNc* substantia nigra pars compacta, *SNr* substantia nigra pars reticulata, *ILT* intralaminar/midline thalamic nuclei, *AM* amygdala, *PPn* pedunculopontine nucleus

some years to be GABAergic, recent electrophysiological, biochemical, and immunocytochemical evidence indicates that this nucleus is EAAergic (Albin et al., 1989a; Mitchell et al., 1991; Robledo and Feger, 1990). The STN has prominent projections (Fig. 1) to the globus pallidus (lateral segment of the globus pallidus in primates), the ventral pallidum, the entopeduncular nucleus (medial segment of the globus pallidus in primates), and substantia nigra (including both the pars compacta and pars reticulata) (Kita and Kitai, 1987; Groenewegen and Berendse, 1990). There are also reciprocal connections between the STN and striatum which appear to be quantitatively small in rodents but may be larger in carnivores and primates (Beckstead, 1983; Parent et al., 1989; Fig. 1).

There are possibly two additional EAAergic afferents to the basal ganglia

(Fig. 1). The intralaminar/midline nuclei project to the striatal complex, the globus pallidus, the ventral pallidum, and the STN (Parent, 1990). Retrograde [^{3}H]D-aspartate tracing studies indicate that some components of the intralaminar/midline complex have an EAAergic projection to the striatum (Fuller et al., 1987). However, Nieoullon and colleagues (1985) have shown that biochemical indices of EAAergic function in the striatum do not decrease after lesions of the parafascicular nucleus, a portion of the midline complex with prominent striatal efferents. No other neurotransmitter has been identified within parafascicular nucleus neurons and these discrepant findings await resolution. The pedunculopontine nucleus (PPN) is another possibly EAAergic afferent of the basal ganglia. The PPN innervates the substantia nigra, the globus pallidus, and entopeduncular nucleus (Parent, 1990). The PPN appears to contain a mixed population of cholinergic and non-cholinergic neurons (Rye et al., 1987). Butcher and colleagues have suggested that the PPN sends cholinergic efferents to its basal ganglia targets (Gould et al., 1989). Lee et al. (1988), however, have found that the non-cholinergic neurons of the PPN tend to innervate basal ganglia structures while cholinergic PPN neurons tend to innervate the thalamus. The findings of Lee et al. (1988) are consistent with the results of Scarnati et al. (1986), who found that PPN induced excitation of nigral neurons is not blocked by scopolamine. While this leaves open the possibility that PPN excitatory neurotransmission might be mediated by nicotinic cholinergic receptors, Scarnati et al. (1986) also found that PPN excitation of the nigra was blocked by EAA antagonists. The findings of Scarnati et al. (1986) are consistent with the existence of EAAergic PPN neurons but further work must be done to identify the neurotransmitter of PPN neurons innervating the basal ganglia.

EAA receptors within the basal ganglia

In common with other classes of neurotransmitter receptors, EAAs exert their effects via receptor subtypes with distinctive physiologic and pharmacologic properties. There are presently four generally accepted and well defined subtypes of post-synaptic EAA receptor (Monaghan et al., 1989; Young and Fagg, 1990). Three of these receptors are ionotropic receptors and are named after their prototype agonists. The α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate (KA) receptors form ligand gated ion channels permeated by monovalent cations and mediate conventional fast neurotransmission. The N-methyl-D-aspartate (NMDA) receptor has unusual properties. It is permeated by both Ca^{++} and monovalent cations, produces a post-synaptic potential with long latency of onset and prolonged duration, exhibits voltage dependent activation, and possesses additional modulatory sites for glycine, polyamines, and phencyclidine ligands. Activation of NMDA receptors is thought to underlie some forms of synaptic plasticity. EAAs also activate a non-ionotropic (metabotropic; MET) receptor that stimulates inositol phospholipid turnover (Sladeczek et al., 1988). In addition to these well defined receptors, we have described an [^{3}H]glutamate binding site that is insensitive to displacement with KA, quisqualate (eliminating both AMPA and MET binding sites), or NMDA. The physiologic identity of this non-NMDA, non-KA,

non-quisqualate (NNKQ) binding site is unknown, but lesion experiments indicate that it is located on striatal neurons (Higgins et al., 1989; Greenamyre et al., 1990).

We have used receptor autoradiography to systematically study the distribution of EAA binding sites in rat basal ganglia (Albin et al., 1991). All assays were done with single concentrations of ligand, and we have assumed that the affinity of binding sites for ligand(s) are invariant from region to region. Tritiated KA and AMPA were used to assay KA and AMPA binding sites. To assay NMDA and MET binding sites, we used [^{3}H]glutamate under selective conditions.

EAA binding sites were found to be distributed heterogeneously within the striatal complex and between non-striatal basal ganglia nuclei (Table 1, Fig. 2). Within the striatal complex, there was a high level of all EAA binding site subtypes. KA binding sites had a significantly higher level in the lateral portion of the dorsal striatum than in the medial portion of the dorsal striatum. NMDA and AMPA binding sites had significantly higher levels in the ventral (nucleus accumbens and olfactory tubercule) portion of the striatal complex than in the dorsal striatum. No other medial-lateral or dorsal-ventral gradients of EAA binding sites were noted within the striatal complex. While we did not find any medial-lateral differences in NMDA binding site distribution within the striatal complex, Monaghan et al. (1988) have found evidence of NMDA binding site inhomogeneity within the dorsal striatum. Specifically, they have suggested that the NMDA binding site exists in either agonist or antagonist preferring conformations and that the relative proportion of these conformations differs between medial and lateral dorsal striatum. The available evidence suggests that the majority of striatal EAA binding sites are post-synaptic though some evidence indicates the presence of pre-synaptic EAA receptors on nigrostriatal dopaminergic terminals and on corticostriate terminals (Greenamyre and Young, 1989; Errami and Nieoullon, 1988; Cheramy et al., 1986).

To assess the relative distribution of EAA binding site subtypes between the non-striatal nuclei of the basal ganglia, we normalized the level of each EAA binding site subtype by expressing levels of EAA binding site subtypes in each non-striatal nucleus as a percentage of striatal binding levels (Table 1). These percentages were compared with one way analysis of variance to assess the relative level of each EAA binding site subtype within the nonstriatal nuclei of the basal ganglia. All EAA binding site subtypes were found within all non-striatal nuclei but the level of all EAA binding site subtypes was lower in the non-striatal nuclei than in the striatal complex. The level of the NMDA binding site subtype was particularly low in all non-striatal nuclei. AMPA and MET binding sites had relatively higher levels in the globus pallidus, ventral pallidum, and subthalamic nucleus. MET binding sites had relatively high levels in the entopeduncular nucleus and substantia nigra (includes both pars compacta and pars reticulata), and NNKQ binding sites had relatively high levels in the globus pallidus, ventral pallidum, entopeduncular nucleus, and nigra. KA binding sites had a relatively high level in the ventral pallidum, subthalamic nucleus, and entopeduncular nucleus. Our results provide evidence of significant heterogeneity of distribution of EAA binding site subtypes within the basal ganglia and indicate that the actions of EAAs within the various nuclei of the basal ganglia

Table 1. Density of excitatory amino acid binding sites in rat basal ganglia. Units are pmol/mg prot (S.E.M.). Percentages are percent of binding in region as percentage of binding in the striatal complex[a]

Region	NMDA	AMPA	MET	KA	NNKQ
Lateral	0.673	2.417	0.694	1.004[1]	1.513
Striatum[b]	(0.016)	(0.031)	(0.053)	(0.172)	(0.193)
Medial	0.676	2.559	0.738	0.958	1.493
Striatum[b]	(0.06)	(0.082)	(0.076)	(0.179)	(0.140)
Dorsal	0.68	2.287	0.734	0.894	1.500
Striatum[c]	(0.016)	(0.105)	(0.035)	(0.091)	(0.167)
Nucleus	1.002	2.712	0.767	0.9843	1.527
Accumbens	(0.039)	(0.286)	(0.084)	(0.091)	(0.133)
Olfactory	1.25	2.583	0.834	1.015	1.373
Tubercule	(0.063)	(0.322)	(0.093)	(0.093)	(0.140)
Ventral	1.127[2]	2.666[2]	0.818	0.997	1.427
Striatum[d]	(0.031)	(0.309)	(0.086)	(0.086)	(0.133)
Striatal	0.903	2.467	0.772	0.975	1.500
Complex					
Globus	0.081	0.626[3]	0.181[3]	0.138	0.533[3]
Pallidus	(0.012)	(0.054)	(0.03)	(0.01)	(0.060)
	9%	25%	23%	14%	36%
Ventral	0.173	0.864[3]	0.363[3]	0.443[3]	0.740[3]
Pallidum	(0.033)	(0.036)	(0.045)	(0.030)	(0.087)
	19%	35%	47%	45%	49%
Entopeduncular	0.064	0.41	0.159[3]	0.233[3]	0.280[3]
Nucleus	(0.006)	(0.010)	(0.030)	(0.037)	(0.027)
	7%	16%	21%	23%	19%
Subthalamic	0.161	0.778	0.377[3]	0.285	0.223
Nucleus	(0.015)	(0.051)	(0.059)	(0.042)	(0.053)
	18%	31%	49%	29%	15%
Substantia	0.112	0.578	0.259[3]	0.193	0.613[3]
Nigra	(0.014)	(0.025)	(0.038)	(0.042)	(0.040)
	12%	23%	34%	20%	41%
Ventral	0.188	0.450	0.11	0.148	0.360
Tegmental Area	(0.031)	(0.030)	(0.051)	(0.047)	(0.053)
	20%	18%	14%	15%	24%

[a] mean of dorsal striatum, accumbens, and olfactory tubercule weighted to correct extent of dorsal striatum

[b] medial and lateral striatum measurements from animals sectioned in coronal plane

[c] mean of lateral and medial striatum in coronal sections averaged with STR from parasagittal sections

[d] mean of nucleus accumbens and olfactory tubercule

[1] lateral greater than medial by paired *t*-test

[2] ventral greater than dorsal striatum by paired *t*-test

[3] relatively higher level of binding for superscripted binding sites than binding sites without superscripts by one way analysis of variance of percentage of complex binding

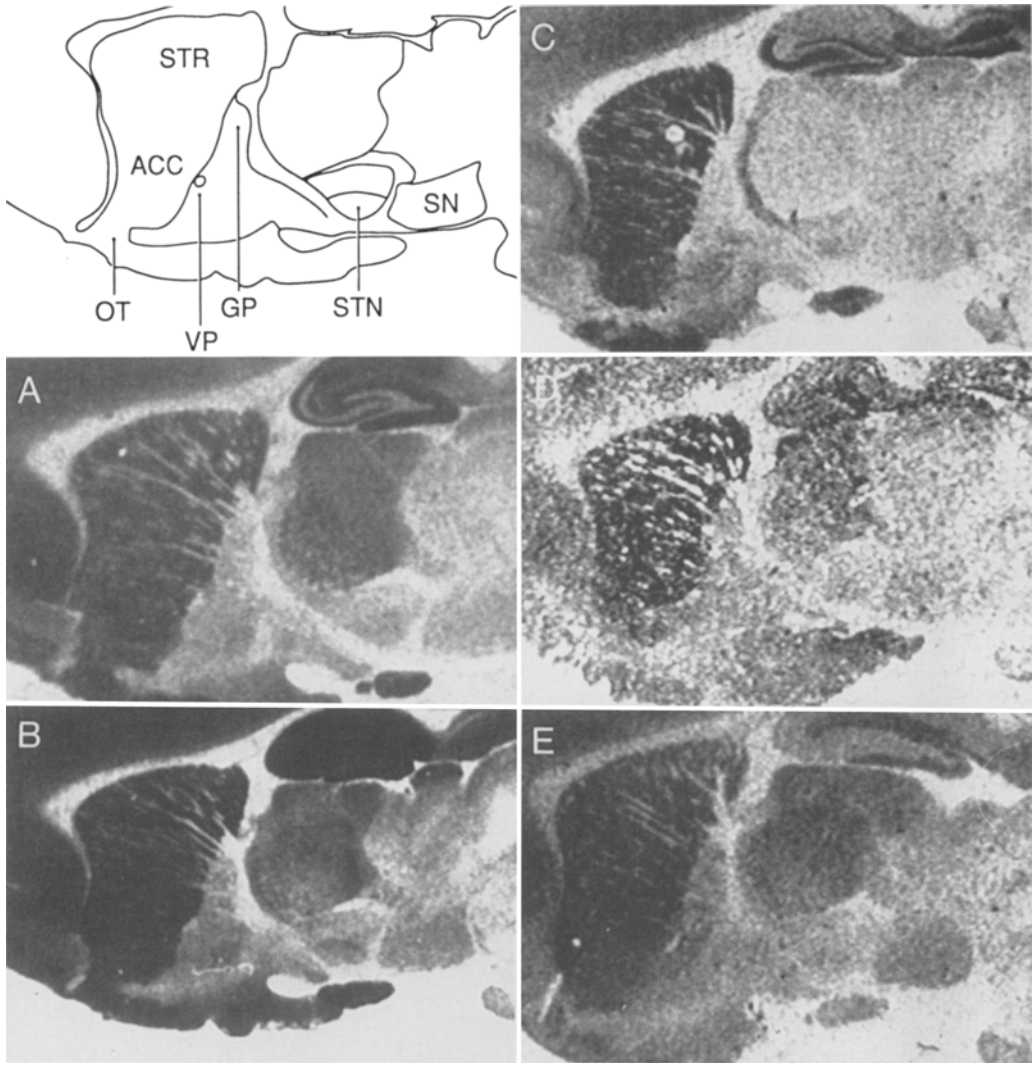

Fig. 2. Parasagittal autoradiographs of excitatory amino acid binding sites in the basal ganglia of the rat. (**A**) NMDA. (**B**) AMPA. (**C**) KA. (**D**) MET; image made by digital subtraction of nonspecific binding from total binding on adjacent sections. (**E**) NNKQ. *STR* dorsal striatum, *ACC* nucleus accumbens, *OT* olfactory tubercule, *VP* ventral pallidum, *GP* globus pallidus, *STN* subthalamic nucleus, *SN* substantia nigra. Magnification of 10x prior to reduction

is likely to be complex. Our discovery of heterogeneous distribution of basal ganglia EAA binding sites probably only hints at the complexity of EAA receptor distribution in the basal ganglia. Molecular cloning studies have shown multiple isoforms of the AMPA receptor and it is likely that multiple isoforms of other EAA receptors will eventually be identified. It would not be surprising if there is a heterogeneous distribution of receptor subtype isoforms between and within the different nuclei of the basal ganglia.

The finding that non-NMDA receptors predominate in the non-striatal nuclei of the basal ganglia has implications for the clinical pharmacology of

Parkinson's disease (PD). A considerable body of evidence indicates that hyperactivity of the subthalamic nucleus and consequent excessive excitation of the pallidum and nigra is an important component of the pathophysiology of PD (Albin et al., 1989b). Blockade of the cortical input to the subthalamic nucleus would decrease the activity of the subthalamic nucleus, pallidum, and nigra. A similar effect could be achieved by blocking the effect of the subthalamic nucleus on the pallidum and nigra. Blockade of non-NMDA EAA receptors in the subthalamic nucleus, pallidum, and nigra might restore the activity of these nuclei towards normal levels. The pharmacology of non-NMDA EAA antagonists is an expanding field and non-NMDA EAA antagonists may prove useful in the symptomatic treatment of PD.

The comparative anatomy of EAA receptors in the striatopallidal complex

It is now generally appreciated that the striatopallidal complex is one of the oldest and most conserved portions of the forebrain. Northcutt (1981) has suggested that a homologue of the striatum was present in all early ancestral vertebrates, and several lines of evidence indicate that a homologue of the striatum is found in many modern vertebrates (Parent, 1986). Among amniotic vertebrates (those possessing an amniotic membrane; reptiles, avians, and mammals), the degree of homology is particularly marked. The hodology, histochemistry, neurotransmitter content, and neuropeptide content of the striatal, pallidal, and nigral homologues exhibit striking similarities in mammals, avians, and reptiles (Reiner and Anderson, 1990; Reiner et al., 1984). Recent studies of receptor distribution in non-mammalian vertebrates have confirmed the marked degree of similarity of the striato-pallidal complex of amniotic vertebrates. Dietl et al. (1988a; 1988b; 1988c) have studied the distribution of muscarinic cholinergic, dopamine, and GABA/benzodiazepine receptors in pigeon (Columba livia) striatopallidal complex and found the distribution of these binding sites to be identical with those seen in mammals. The distribution of benzodiazepine and muscarinic cholinergic binding sites in turtle (Pseudemys scripta) forebrain shows a pattern of binding in the striatopallidal homologue similar to that seen in mammals and avians (Schlegel and Kriegstein, 1987).

We have examined the distribution and pharmacology of some EAA binding site subtypes in turtle and pigeon brain. We have concentrated on NMDA binding and characterized the NMDA binding site using both [^{3}H]glutamate binding under selective conditions and the non-competitive NMDA ligand, [^{3}H]MK-801 (Sakurai et al., 1990; Young et al., 1990). Our studies indicate that in both pigeon and turtle brain, NMDA binding sites possess properties similar to those found in mammalian brain. In the striatopallidal complex of both pigeons and turtles (Fig. 3), the pattern of distribution of NMDA binding sites was similar to that seen in mammals, i.e., high levels of NMDA binding sites in the striatal homologue and lower levels in the pallidal homologue. We have obtained similar results with assays for KA binding sites and quisqualate binding sites (a combination of both AMPA and MET binding sites), though we have not extensively characterized the properties of these assays in either pigeon or turtle brain (Young et al., 1990; Richfield et al., 1988).

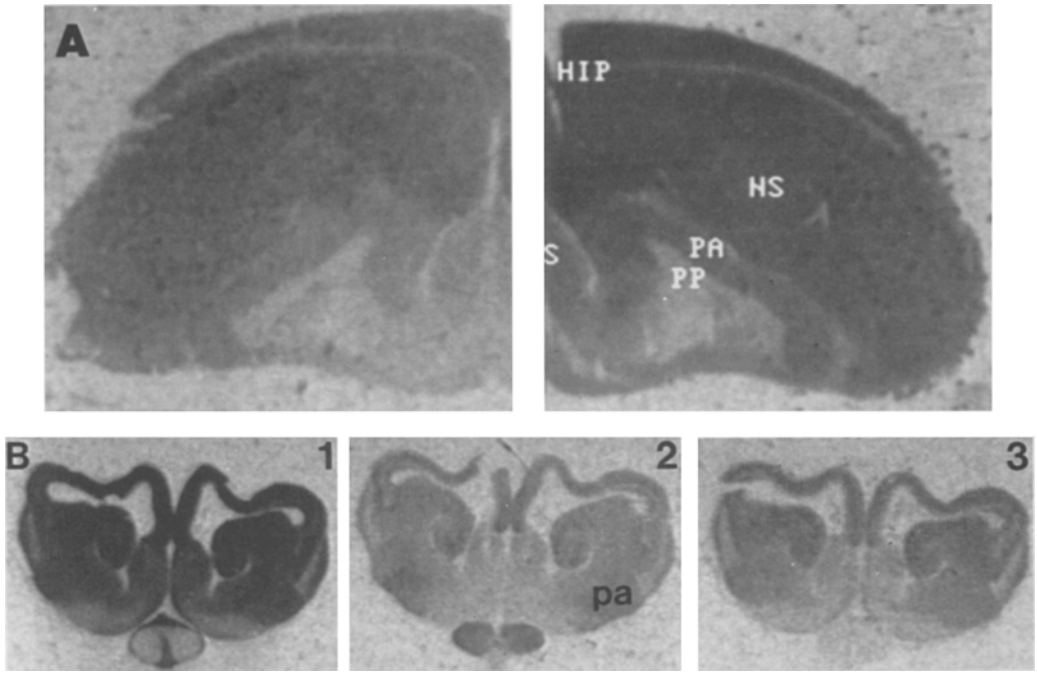

Fig. 3. Autoradiographs of NMDA binding sites in the striatopallidal homologues of pigeon (**A**) and turtle (**B**). (**A**) Pigeon: Right side is [^{3}H]MK-801 binding and left-side is NMDA-displaceable [^{3}H]glutamate binding. *PA* paleostriatum augmentatum (homologue of striatum in pigeon). *PP* paleostriatum primitivum (homologue of globus pallidus in pigeon). (**B**) Turtle: (*1*) NMDA-displaceable [^{3}H]glutamate binding, (*2*) strychnine-insensitive [^{3}H]glycine binding, (*3*) [^{3}H]MK-801 binding, *pa* paleostriatum augmentatum

EAA receptors in human basal ganglia disease

Interest in the role of EAA receptors in human basal ganglia disease has been driven by the possibility that EAA receptors in general, and the NMDA receptor in particular, may be mediators of neuronal death in human neurodegenerative diseases. This idea remains the most popular hypothesis to explain the pathogenesis of Huntington's disease (HD; DiFiglia, 1990). Recent reports that NMDA antagonists block both MPTP (Turski et al., 1991) and amphetamine induced (Sonsalla et al., 1989) lesions of the nigrostriatal dopaminergic pathway raises the possibility that NMDA receptors may be involved in the pathogenesis of Parkinson's disease (PD).

To explore the potential role of EAA receptors in the pathogenesis of HD and PD we have investigated the alterations in EAA binding sites in HD striatum and PD substantia nigra. In HD, we have studied the striatum of controls and HD victims with a variety of assays for EAA receptor subtypes. In the most recent study, adjacent sections from fourteen HD and twelve control brains were assayed for AMPA, KA, NMDA, and MET binding sites (Dure et al., 1991). In HD striatum, the level of all binding sites was reduced (Fig. 4). KA, AMPA, and NMDA binding sites were significantly reduced by fifty to sixty percent compared to controls while MET binding was reduced by thirty-one percent and

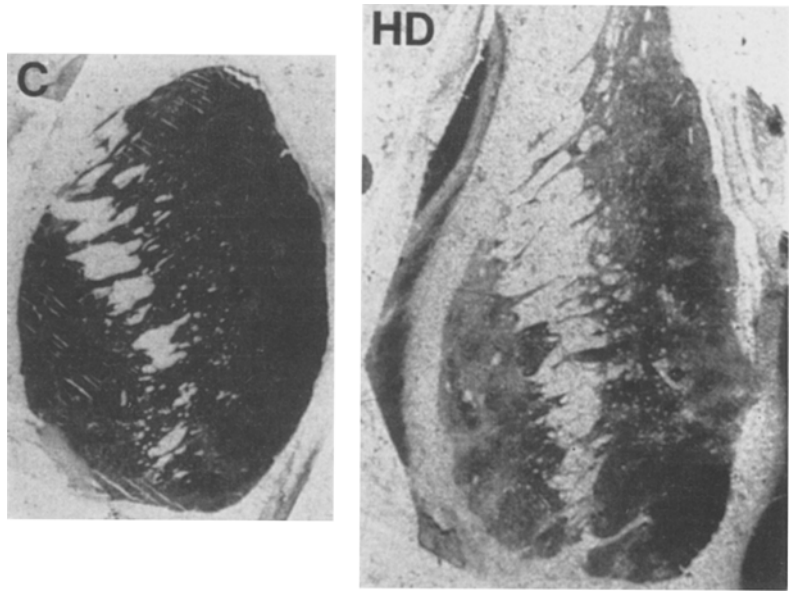

Fig. 4. Autoradiographs of AMPA binding in human control (*C*) and Huntington's disease striatum (*HD*). The amount of binding in HD striatum is reduced and the pattern of ligand binding has become quite inhomogeneous

NNKQ binding sites were reduced by twenty-six percent. The reductions in MET and NNKQ binding were not statistically significant. The pattern of binding site loss was striking in that there was clear inhomogeneity of binding site loss within the striatum (Fig. 4). Parallel study of EAA binding sites within neocortex revealed no differences between HD and control brains. Our results are consistent with the hypothesis that EAA receptors mediate neuronal death in HD but do not provide unequivocal evidence that one EAA receptor subtype is more likely to be important than another in mediating neuronal death.

NMDA, AMPA, MET, and NNKQ binding sites were measured in PD substantia nigra (Penney et al., 1990). As expected from animal studies, the level of binding was relatively low in substantia nigra. NMDA binding sites were significantly reduced in the pars compacta and pars reticulata of PD brains compared to controls while AMPA and NNKQ binding sites were reduced in the pars compacta and MET binding sites were unchanged in either pars compacta or pars reticulata. At very least, these results suggest that NMDA, AMPA, and NNKQ binding sites are located on dopaminergic substantia nigra neurons. This inference is consistent with data suggesting that EAA receptors are located on nigral dopaminergic neurons and may be involved in regulating the activity of dopaminergic neurons (Mount et al., 1990; Araneda and Bustos, 1989; Kalivas et al., 1989). These results are also consistent with a putative role for EAA receptors in mediating neuronal death in PD. As with HD, this data does not provide unequivocal evidence that an EAA mediated process is involved in the pathogenesis of HD.

Acknowledgements

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