Receptors in the Basal Ganglia

Mark Guttman

ABSTRACT: The study of neurotransmitter receptors aids in the understanding of the normal anatomy, pharmacology, therapeutics and pathophysiology of disease processes involving the basal ganglia. Receptors may be studied *in vitro* by homogenate binding experiments, enzyme analysis or quantitative autoradiography and *in vivo* with positron emission tomography. In the substantia nigra (SN), receptors have been identified for somatostatin, neurotensin, substance P, glycine, benzodiazepine and GABA, opiates, dopamine, angiotensin converting enzyme (ACE) and serotonin. The striatum has receptors for dopamine, GABA and benzodiazepines, acetylcholine, opiates, substance P, glutamate and cholecystokinin. GABA and benzodiazepine receptors are also located in the globus pallidus. In Parkinson's disease, striatal dopamine D-2 receptors are elevated in patients that have not received L-DOPA therapy. This supersensitivity is reversed with agonist therapy. Muscarinic binding to cholinergic receptors seems to correlate with dopamine receptors. Delta opiate receptors are increased in the caudate and mu binding is reduced in the striatum. In the SN of patients with Parkinson's disease, there is reduced binding of somatostatin, neurotensin, mu and kappa opiates, benzodiazepine and GABA and glycine. In Huntington's disease, there is reduced binding of GABA and benzodiazepines, dopamine, acetylcholine, glutamate and CCK. There is increased binding of GABA in both the SN and globus pallidus. Glycine binding is increased in the substantia nigra and ACE is reduced.

RÉSUMÉ: Récepteurs dans les noyaux gris centraux. L'étude des récepteurs des neurotransmetteurs nous aide à comprendre l'anatomie normale, la pharmacologie, la thérapeutique et la pathophysiologie des processus pathologiques touchant les noyaux gris centraux. Les récepteurs peuvent être étudiés *in vitro* par des épreuves de liaison sur homogénat, l'analyse enzymatique ou l'autoradiographie quantitative et *in vivo* par la tomographie par émission de positron.

Des récepteurs pour la somatostatine, la neurotensine, la substance P, la glycine, les benzodiazépine et le GABA, les opiacés, la dopamine, l'enzyme de conversion de l'angiotensine (ECA) et la sérotonine ont été identifiés dans la substance noire (SN). Le striatum possède des récepteurs pour la dopamine, le GABA et les benzodiazépines, l'acétylcholine, les opiacés, la substance P, la glutamate et la cholécystokinine. Il y a également des récepteurs pour le GABA et les benzodiazépines dans le globus pallidus.

Dans la maladie de Parkinson, le nombre de récepteurs dopaminergiques D-2 au niveau du striatum est augmenté chez les patients qui n'ont pas été traités par la L-DOPA. Cette hypersensibilité disparaît lors de la thérapie par des agonistes de la L-DOPA. La liaison muscarinque aux récepteurs cholinergiques semble faire corrélation avec les récepteurs dopaminergiques. Le nombre des récepteurs aux opiacés de type delta est augmenté dans le noyau caudé et la liaison aux opiacés de type mu est diminuée dans le striatum. Il y a une diminution de la liaison de la somatostatine, de la neurotensine, des opiacés mu et kappa, des benzodiazépines, du GABA et de la glycine dans la SN de patients atteints de la maladie de Parkinson. Dans la maladie de Huntington, il y a une diminution de la liaison du GABA, des benzodiazépines, de la dopamine, de la muscarine, du glutamate et la CCK. Il y a augmentation de la liaison du GABA dans la SN et également dans le globus pallidus. La liaison de la glycine est augmentée dans la SN et l'ECA est diminué.

Can. J. Neurol. Sci. 1987; 14:395-401

Neurotransmitter receptors play an essential role in neural transmission and the functional integrity of the brain. The study of these receptors aids in the understanding of normal anatomy, pharmacology and therapeutics as well as the pathophysiology of disease processes involving the basal ganglia. The field of receptors has evolved into a rapidly growing area of research. The purpose of this article is to provide a review of the subject to help in the understanding of the current areas of research, and the role of receptors in movement disorders.

Receptors are protein macromolecules that are located in cell membranes, cytoplasm or nucleus. Most drugs are thought to act on drug or neurotransmitter receptors. The activation of receptors may initiate a second messenger system or may lead to electrical discharge and signal propagation in post-synaptic cells. Many receptors are on post-synaptic or pre-synaptic membranes. The latter may be involved in a feedback inhibition system and are called autoreceptors. Each type of receptor may have many subclasses. Activation of one class of receptors may oppose the physiological function of the neurotransmitter acting at a different site. To complicate the issue even more, there may be more than one affinity state for each subclass of receptor. This will be discussed in more detail in the section

From the Department of Medicine, Division of Neurology, University of British Columbia, Vancouver
Reprint requests to: Dr. Mark Guttman, Department of Medicine, Division of Neurology, 2211 Wesbrook Mall, Vancouver, B.C., Canada V6T 1W5

pertaining to the individual neurotransmitter systems.

There are many receptors located in the basal ganglia that are potentially involved in the control of movement. These include receptors for dopamine, gamma amino butyric acid (GABA), benzodiazepines, opiates, acetylcholine, glutamic acid, glycine and peptide neurotransmitters. While some of these have been investigated in detail in both humans and animals, others have had very preliminary studies in the latter only. The methods of analysis and the species used have varied to such a great extent that it is often very difficult to compare data.

Methods of Analysis

Neurotransmitter receptors may be studied by *in vitro* and *in vivo* techniques.[1] Binding studies yield an index of receptor density (B_{max}) and a dissociation constant (K_D) that is inversely proportional to the affinity of the ligand. Pathological states can be assessed in terms of change in receptor numbers or change in the affinity of the ligand. If the K_D remains constant, then one may conclude that the disease process has changed the receptor density.

In vitro tissue homogenate binding may be assessed by a radioreceptor assay using tightly bound antagonists. With this method, receptors that have both high and low affinity states are measured together. If one uses an agonist, it is possible to assess only a high affinity site and thus fail to obtain a true total receptor density. It is therefore better to use antagonists whenever possible to study a total receptor number. High and low affinity states change with the freezer life span of the tissue and experimental variables such as ionic concentrations and the addition of guanine nucleotide. This makes it impractical to assess the various affinity states in post-mortem human tissue at this time. Animal work is now being pursued to study alterations in high and low affinity states of receptors such as the dopamine receptor induced in pathological states.

Radioreceptor assays may be performed with a filtration or centrifugation technique. Saturation analysis attempts to measure the specific binding of a tritiated ligand to the receptor, first by measuring the total binding to the tissue and then subtracting the nonspecific binding in the presence of an excess of cold antagonist. The saturation binding curve is a function of the number of receptors and the concentration of tritiated ligand available. Scatchard analysis transforms this data to a linear plot with K_D as the negative slope of the line and B_{max} as the x intercept. Filtration methods enable one to process a large number of samples but has the disadvantage of losing protein (and receptors) through the washing and filtration process. Furthermore, an exact measurement of the free concentration of the ligand is not possible and may lead to error in the calculations due to depletion by nonspecific binding sites.[2] Centrifugation assays are more time consuming, but both of these potential problems are eliminated.

Tissue homogenate studies give a high degree of accuracy, but lack in anatomical precision. Autoradioagraphic analysis of tissue slices provides improved anatomical resolution of receptor location.[3] The application of varying concentrations of ligand, in addition to the assessment of specific binding, allows for the calculation of the binding indices. Computerized grain counting analysis has improved the accuracy of the quantification with this technique. The anatomical localization greatly improves with this technique, but the accuracy of the binding estimate does not approach the tissue homogenate method. Recently, animal studies have been performed with the *in vivo* administration of isotope providing a model for the validation of PET binding studies.[4]

Positron emission tomography (PET) has been used to study neurotransmitter receptors.[5] The aim of PET is to provide a quantitative *in vivo* analysis of receptors.[6] After the injection of positron emitting ligands, one can measure the regional radioactivity of the brain. The previous disadvantages of post-mortem artifacts, difficulty in matching patients and problems with brain acquisition, are all surpassed. The initial receptor studies were analyzed by comparing the ratios of radioisotope concentration in areas that are rich in receptors (basal ganglia) to those that are devoid of receptors (cerebellum). Recently, new approaches for the saturation analysis of receptors[7] and tracer kinetic analysis[8] have provided measurements that may be compared with homogenate and autoradiographic techniques.

Dopamine Receptors

Dopamine receptors are present in the substantia nigra, caudate and putamen. There are two classes of dopamine receptor, D_1 and D_2.[9] The D_1 site activates adenyl cyclase and the D_2 site either inhibits or does not affect this second messenger system. The D_2 site has a physiological role in the control of motor functions. The D_1 receptor, on the other hand, does not have a well defined physiologic role, it may be involved in modulating the D_2 system. This interaction and the clinical significance of the two sites are the topics of another paper in this volume (Beaulieu) and will not be discussed here.

There are high and low affinity states that have been identified for both classes of dopamine receptors. These affinity states are appreciable only when agonists are used in the binding studies; antagonists do not recognize the difference. The proportion of high and low affinity states may be changed *in vitro*, depending on experimental conditions. It is not known what causes the conversion *in vivo* between the two states, though neuromodulators have been implicated. It has been suggested that the post-synaptic D_2 state is normally functional in the low affinity state in the striatum. Pre-synaptic autoreceptors most likely function in the high affinity state.[10]

D_2 Dopamine Receptor

This site has been analyzed *in vitro* by homogenate binding studies[11] and quantitative autoradiography.[1] Most of this work has employed high affinity radioactive neuroleptics. Spiperone, a butyrophenone, is a suitable ligand for this site but has the disadvantage of binding to S_2 serotonin receptors in the same concentration range. In the striatum this is not a major problem because of the lack of S_2 receptors in this location. Substituted benzamides have a higher degree of specificity at the D_2 site. *In vivo* PET studies have used spiperone derivatives and raclopride[7] for dopamine receptor binding studies.

It is difficult to assess the exact cellular location of D_2 binding sites. Anatomical localization is suggested by indirect means with lesions at distant sites that are known to send processes to the area of interest. If receptor sites drop out or increase in number, the relationship of the distant neuronal population to the site under study may be inferred. Until histofluorescent studies are available (after receptor purification is achieved), this is the best that can be anticipated. D_2 receptor sites are possibly both pre and post-synaptic. The dopaminergic neu-

https://doi.org/10.1017/S0317167100037793 Published online by Cambridge University Press

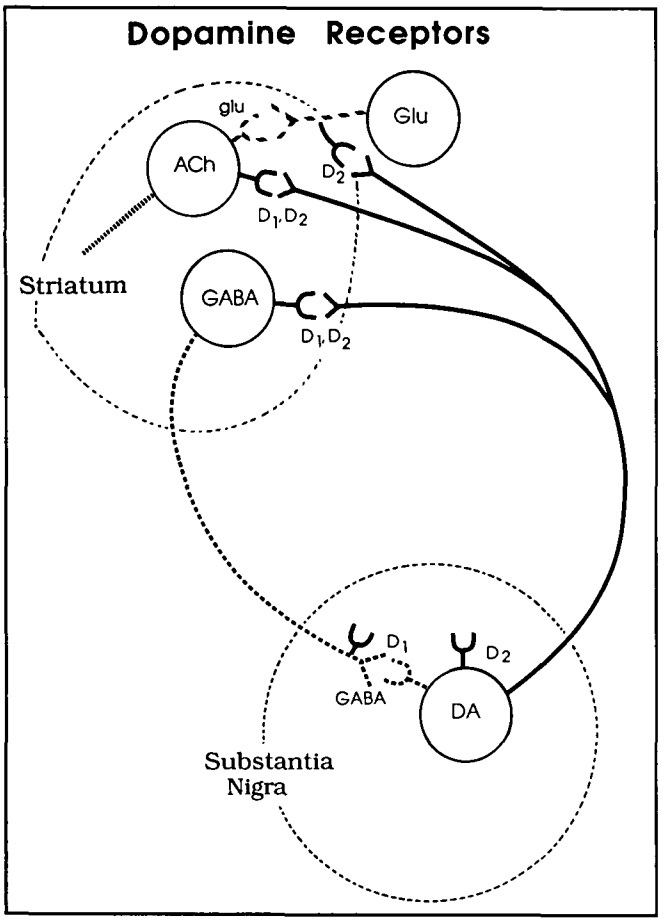

Figure 1 — Dopamine D_1 and D_2 receptor sites in the striatum and substantia nigra. Legend: DA - dopamine, ACh - aceytlcholine, Glu - glutamate, GABA - gamma amino butyric acid.

rons of the pars compacta of the substantia nigra send axons to the striatum. The exact termination of these axons has been thought to be on two specific neural populations.[12] One site is that of the interneurons of the striatum. The other site is on the pre-synaptic axon of glutaminergic neurons from the cerebral cortex, as judged from cortical lesion studies. As many as 40% of the receptors may be at this location, suggesting a dopaminergic role in the cerebral modulation of movement. Recently, this site for D_2 receptors has been questioned[13] with the use of quantitative autoradiography. In the substantia nigra, D_2 sites are found in the pars compacta. These are most likely autoreceptors on dopaminergic cell bodies and dendrites as judged by human studies in patients with Parkinson's disease.[14] (See Figure 1)

D_2 dopamine receptors have been found to be altered in pathological conditions. Supersensitivity, defined as an increase in receptor density, can be induced by denervating the receptor by anatomical lesions or with neuroleptics.[15] Striatal D_2 dopamine receptors have been found to be increased in patients with Parkinson's disease who have not been treated with dopamine agonists.[16,17,18] This supersensitivity is reversed if patients are treated with L-dopa, but the density is not reduced below the level of controls. The receptor density does not decrease progressively with the duration of time the patient is on agonist therapy or with the progress of the disease.[19] This suggests that the late onset reduction of benefit seen with agonist treatment is not due to loss of receptors as previously suggested by others.[18]

In Parkinson's disease the D_2 density is also reduced in the substantia nigra. This again suggests that the location of these sites is on the dopaminergic cell and its processes. In Progressive Supranuclear Palsy these receptors are decreased in both the striatum and the substantia nigra.[20] This has also been confirmed semi-quantitatively *in vivo* with PET studies using ^{76}Br-bromospiperone.[21] This may be the reason for the failure of agonist therapy in this condition. In Shy Drager syndrome there has also been a reduction of D_2 receptors found in the substantia nigra.[22] In Huntington's disease there is a reduction of sites in the striatum.[23] In this condition, there is a normal dopamine content in the striatum and coupled with a reduction in the numbers of receptors, there may be increased dopaminergic transmission in the surviving neurons. This reduction in striatal D_2 receptors is reversed with neuroleptic treatment (Seeman personal communication). Schizophrenic patients have been shown to have an increased density of the D_2 receptors but there is some controversy if this is a result of neuroleptic treatment or a primary manifestation of the disease process.[24]

D_1 Dopamine Receptor

This class of dopamine receptors has been analyzed *in vitro* with the use of tritiated antagonists such as flupenthixol and more recently SCH 23390. The latter has a much higher degree of specificity. D_1 receptors also have a high and low affinity state and the significance of this is unknown at this time.

Striatal D_1 receptors are thought to be located on the post-synaptic interneurons. In the pars reticulata of the substantia nigra, these receptors are found on pre-synaptic processes of GABAergic neurons that originate in the striatum.[25] The evidence for this comes from animal studies in which the striatum was lesioned with kainic acid and binding studies were performed in nigral homogenates. This suggests that there is modulation of the GABAergic neurons by the dopaminergic cells of the substantia nigra pars compacta. (Figure 1)

The D_1 dopamine receptor has been reported to be abnormal in several diseases. In Parkinson's disease, striatal sites are increased.[26] It is unclear if this is reversed with treatment. In Huntington's disease, striatal and substantia nigra pars reticulata D_1 receptors are reduced.[23] This is further evidence for the proposed nigral site of this receptor.

GABA/Benzodiazepine Receptors

Basal ganglia GABA and benzodiazepine receptors are located in the caudate, putamen, substantia nigra and globus pallidus. This receptor has many sites that interact with each other. The primary GABA receptor is associated with a benzodiazepine binding site. The GABA site is centered on a chloride channel that is activated with receptor binding. Benzodiazepine site activation facilitates GABA binding at the primary site. Barbiturates may also bind to the benzodiazepine site. The GABA site has high and low affinity states.[1] The benzodiazepine site has two classes, type I or type II. In the striatum, GABAergic neurons are interneurons and are also part of the output pathway of the basal ganglia. These striatal neurons project to the globus pallidus pars externa and interna as well as the substantia nigra pars reticulata. Pathological alterations in the GABA content of the brain have been postulated in Huntington's disease, epilepsy and spasticity. There is a potentially impor-

https://doi.org/10.1017/S0317167100037793 Published online by Cambridge University Press

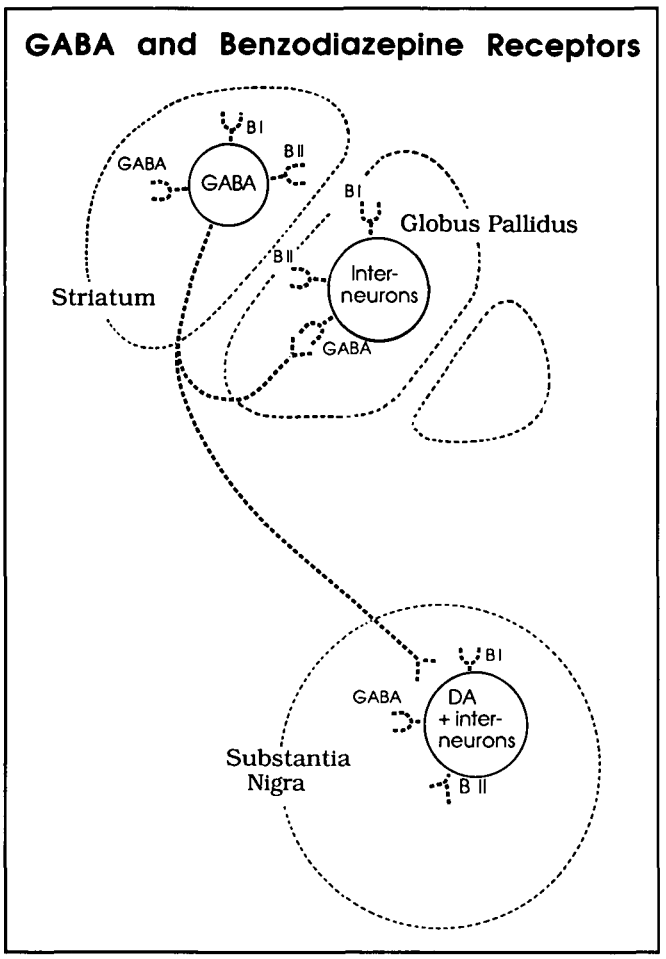

Figure 2 — GABA and benzodiazepine receptor sites in the striatum, globus pallidus and substantia nigra. Legend: BI - benzodiazepine I site, BII - benzodiazepine II site, GABA - gamma amino butyric acid, DA - dopamine.

tant interaction with the dopamine system that has not been clearly defined.

GABA receptor

This receptor may be measured with the specific antagonist bicuculline.[1] Most reports make the use of agonist binding with labelled muscimol or GABA. Anatomically, it is again difficult to confirm the exact cellular location of the receptors in the basal ganglia. GABA receptors are thought to be found on interneurons of the caudate, putamen, globus pallidus externa and interna as well as the substantia nigra pars reticulata and possibly pars compacta.[27] Lesion studies in rats have suggested that the GABA receptor has a post-synaptic location in the substantia nigra pars reticulata.[27] There is also indirect evidence that some GABA sites are on dopaminergic cells in the pars compacta.[28] The exact location of receptors in the striatum is unknown. It is possible that there are both pre-synaptic and post-synaptic sites on the interneurons. In the pallidum, the sites are thought to be post-synaptic. (Figure 2)

GABA receptors have been studied in pathological states. Binding of this neurotransmitter has been of interest in Huntington's disease because of the decrease in GABA content of the striatum. GABA binding has also been found to be reduced in the caudate and putamen of post-mortem tissue from patients with this condition.[29,30,31] In the pallidum and substantia nigra pars reticulata, there is increased binding suggesting a supersensitivity. In Parkinson's disease, GABA binding has been found to be reduced in the substantia nigra.[28,32] The authors have postulated a role of the GABA system in modulating the dopamine output of this region. There is presently no way of distinguishing cause and effect.

Benzodiazepine Receptors

Two types of benzodiazepine receptors have been identified by the selective binding of different classes of agonist compounds.[33] Labelled flunitrazepam will bind to the sites equally. Type I sites bind Beta-carboline derivatives (BCCE) selectively and type II bind triazolopyridazine derivatives (CL218872). PET studies with the benzodiazepine antagonist R015-1788 have been reported.[34] The distribution of the receptors in the striatum and pallidum seems to parallel GABA receptors. In the substantia nigra however, there is indirect evidence for the differential localization of these types. It has been suggested that type I sites are post-synaptic and are found on dopaminergic neurons. Type II sites are pre-synaptic to the dopaminergic neurons, but post-synaptic to the striatal nigral fibres, suggesting localization to interneurons in the pars reticulata.[35] These conclusions are taken from studies in rats after sequential lesions had been made in the striatum and substantia nigra.

Benzodiazepine receptor alteration has been documented in disease states. In Huntington's disease there is reduction in type I and II sites in the striatum. In pallidum there is an increase in both types,[29,31] and in the substantia nigra there is an increase in type II sites in animal models.[35] In Parkinson's disease there is a reduction in the type I density in substantia nigra.[14]

Opiate Receptors

Opiate receptors are found in the caudate, putamen, globus pallidus and substantia nigra in the basal ganglia. There are many classes of receptors including mu, lambda and kappa.[36] There are differential effects of various agonists and antagonists in this system. The mu site is activated by the agonists met-enkephalin, morphine and DADL and inhibited by the antagonists naloxone and ICI154129. The lambda site binds the agonists leu-enkephalin and DALA and the antagonists ICI154129 and naloxone. The kappa site is characterized by binding the agonists dynorphin and bremazocine. Carfentanil has been labelled with positron emitting ^{11}C and has been used to identify opiate receptors *in vivo*.[5] The role of opiates in the function of the basal ganglia has been the subject of much recent interest. It has been shown that striatal neurons may contain both GABA and opiate-like immunoreactivity.[37] This has lead to the speculation that opiates may block GABA release and modulate the basal ganglia outflow pathway.

The anatomical localization of these receptors has depended largely on lesion studies in animals. It has been suggested that mu sites are found in patches in the striatum and that the lambda sites are found diffusely in this region.[38] It has been proposed that striatal mu and lambda receptors are partially on the presynaptic axons of nigral dopaminergic neurons.[39] In the pallidum and substantia nigra pars reticulata, lesion studies suggest that some of the mu and lambda sites are on presynaptic terminals of striatofugal neurons,[37] while others are on dopa-

https://doi.org/10.1017/S0317167100037793 Published online by Cambridge University Press

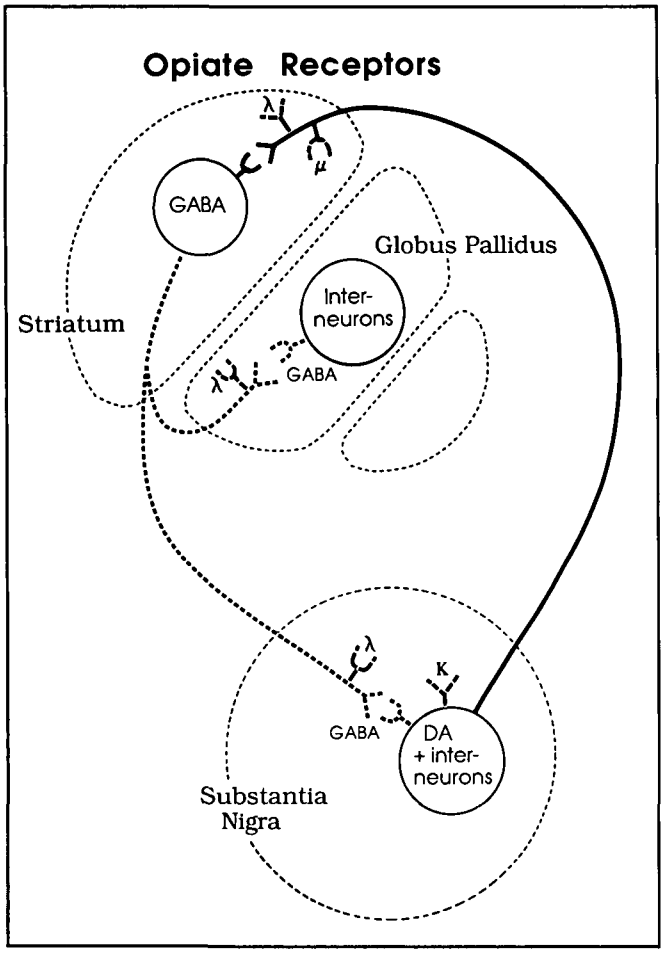

Figure 3 — Opiate receptor sites in the striatum, globus pallidus and substantia nigra. Legend: Lambda, kappa and mu sites are labelled with Greek letters, GABA - gamma amino butyric acid, DA - dopamine.

minergic neurons.[14] Kappa sites are located in the substantia nigra pars reticulata in rats.[36] It has been postulated from post-mortem studies of Parkinsonian tissue, that the kappa sites are on dopaminergic neurons in the substantia nigra.[14] It is unclear at this time what the exact anatomical relationship is for the different classes of opiate receptors and the role of these peptides in the modulation of the basal ganglia. (Figure 3)

In an animal model of Huntington's disease, Abou-Khalil et al have found a reduced binding for the lambda site in pallidum and substantia nigra pars reticulata.[37] In Parkinson's disease, both a reduction in striatal lambda binding[40] and an increase in this class of receptors has been reported.[18] In the substantia nigra in patients with this condition, a reduction in kappa and mu binding has been found.[14]

Muscarinic Receptors

Acetylcholine receptors in the basal ganglia are of the M_2 type. The antagonist 3-quinuclidinyl benzilate (QNB) is used in binding assays.[41] These sites are on interneurons in the striatum. In Huntington's disease, the striatal receptor density is reduced.[31] In Parkinson's disease, there are conflicting reports. Rinne and coworkers suggest that there is a bimodal distribution of receptor binding depending on the dopamine receptor content.[18] The interdependence of these two systems is not surprising in view of the roles of the two transmitter systems in the basal ganglia.[42]

Glutamate/Aspartate Receptors

Glutamate and aspartate are excitatory amino acids that are the putative neurotransmitters of the corticostriatal pathway. Their distribution in the brain is diffuse and they are thought to be the major excitatory transmitters involved in cortical transmission. There are at least three types of receptors for this system.[43] These include the NMDA site, the kainic acid site and the quisqualate site. It has been recently suggested that the NMDA site is not the receptor mediating the corticostriatal system.[44] Using tritiated glutamate as a ligand, a reduction in binding sites has been found in the striatum and cortex of patients with Huntington's disease.[45] The study of the glutamate/aspartate system is of great interest since kainic acid lesions in the striatum are used as an animal model for this condition. The potential use of glutamate receptor antagonists in the prevention and treatment of patients with Huntington's disease is presently being considered.

Glycine Receptors

Glycine is an inhibitory amino acid that is found predominantly in the spinal cord but also occurs in the substantia nigra, inferior olive and cortex. Its exact role in neuromodulation is unknown. Glycine binding is defined by the antagonist strychnine. These sites are thought to be located on dopaminergic cell bodies or dendrites. In Parkinson's disease there is reduced binding in the substantia nigra, while in Hungtington's disease there is increased binding. It has been suggested that this transmitter modulates dopaminergic neurons by inhibiting firing and dopamine release.[46]

Peptide Receptors

Peptides have been suggested as putative neurotransmitters in the basal ganglia. Neurotensin, somatostatin, angiotensin converting enzyme, substance P and cholecystokinin receptors have been reported in this region.

Neurotensin This peptide modulates the dopamine system by enhancing dopamine release. Using tritiated neurotensin as a ligand, receptors have been found in the substantia nigra. In patients with Parkinson's disease, these sites are reduced suggesting a location on dopaminergic neurons.[14,47]

Somatostatin Somatostatin also acts as a neuromodulator by increasing dopamine release. Binding studies in rats,[48] humans and monkeys[49] have shown receptor sites in the striatum and substantia nigra. Using tritiated somatostatin, parkinsonian patients have been shown to have a reduced number of binding sites in the substantia nigra.[14] This suggests that the receptor location is on the dopaminergic cell body or dendrites.

Angiotensin Converting Enzyme (ACE) This enzyme has been found in the striatum, pallidum and substantia nigra, and its physiological role is unknown. Strittmatter and colleagues have suggested that ACE binding is present on presynaptic terminals of striatonigral fibres and may be useful in identifying this pathway.[50] Injection of toxins into the striatum causes loss of these sites. The binding sites have been studied with tritiated captopril and the density is not altered in patients with Parkinson's disease.[14]

Substance P This peptide has been found in the rat striatum and its role may be to increase dopaminergic transmission.[51]

https://doi.org/10.1017/S0317167100037793 Published online by Cambridge University Press

Quirion et al have postulated that tritiated substance P may be used to deliniate the nigrostriatal pathway.

Cholecystokinin Using labelled CCK, binding sites have been identified on neurons in the basal ganglia. In Huntington's disease, CCK sites are reduced in the cortex and striatum.[52] The significance is not known at this time.

Summary

The field of receptors is growing at a very fast rate. New sites are being identified and new techniques to analyze them are being used *in vivo* and *in vitro*. It is presently very difficult to assess the numerous studies in the literature because of the differing methodology used. Perhaps future changes in the *in vitro* methodology with the development of antisera to receptors and *in vivo* advances in PET will allow us to answer the many biological questions that have been asked concerning receptors in the basal ganglia.

References

1. Young AB, Frey KA, Agranoff BW. Receptor Assays: *In vitro* and *in vivo*. *In*: Phelps M, Mazziotta J, Shelbert H, eds. Positron Emission Tomography: Priniciples and Applications for the Brain and Heart. New York: Raven Press, 1986: 73-111.
2. Seeman P, Ulpian C, Wreggett KA, et al. Dopamine receptor parameters detected by [^{3}H] spiperone depend on tissue concentration: analysis and examples. J Neurochem 1984; 43: 221-235.
3. Lear JL. Principles of single and multiple radionuclide autoradiography. *In*: Phelps M, Mazziotta J, Shelbert H, eds. Positron emission tomography and autoradiography: principles and applications for the brain and heart, New York: Raven Press, 1986: 197-235.
4. Bennett JP, Wooten GF. Dopamine denervation does not alter *in vivo* ^{3}H-spiperone binding in rat striatum: implications for external imaging of dopamine receptors in Parkinson's disease. Ann Neurol 1986; 19: 378-383.
5. Wagner HN Jr. Images of the brain: past as prologue. J Nucl Med 1986; 27: 1929-1937.
6. Perlmutter JS, Raichle ME. *In vitro* or *in vivo* receptor binding: where does the truth lie? Ann Neurol 1986; 19: 384-5.
7. Farde L, Hall H, Ehrin E, et al. Quantitative analysis of D_2 dopamine receptor binding in the living human brain by PET. Science 1986; 231: 258-61.
8. Huang SC, Barrio JR, Phelps ME. Neuroreceptor assay with positron emission tomography: equilibrium versus dynamic approaches. J Cereb Blood Flow Metab 1986; 6: 515-521.
9. Kebabian JW, Calne DB. Multiple receptors for dopamine. Nature 1979; 277: 93-93.
10. Seeman P, Grigoriadis D, George SR, et al. Functional states of dopamine receptors. *In*: Woodruff GN, Creese I, Cessa GL, et al eds. Dopaminergic Systems and Their Regulation. London: MacMillan Press. 1984.
11. Seeman P. Brain dopamine receptors. Pharmacol Review. 1980; 32: 229-313.
12. Kornhuber J, Kornhuber ME. Presynaptic dopaminergic modulation of cortical input to the striatum. Life Sci 1986; 39: 669-674.
13. Trugman JM, Geary WA II, Wooten GF. Localization of D-2 dopamine receptors to intrinsic striatal neurons by quantitative autoradiography. Nature 1986; 323: 267-269.
14. Uhl GR, Hackney GO, Torchia M, et al. Parkinson's disease: nigral receptor changes support peptidergic role in nigrostriatal modulation. Ann Neurol 1986; 20: 194-203.
15. Staunton DA, Magistetti PJ, Koob GF, et al. Dopaminergic supersensitivity induced by denervation and chronic receptor blockade is additive. Nature 1982; 299: 72-74.
16. Lee T, Seeman P, Rajput A, et al. Receptor basis for dopaminergic supersensitivity in Parkinson's disease. Nature 1978; 273: 59-61.
17. Guttman M, Seeman P. L-dopa reverses the elevated density of D_2 dopamine receptors in Parkinson's diseased striatum. J Neural Trans 1985; 64: 93-103.
18. Rinne UK. Brain neurotransmitter receptors in Parkinson's disease. *In*: Marsden CD, Fahn S, eds. Movement Disorders. London: 1982, 59-74.
19. Guttman M, Seeman P, Reynolds, et al. Dopamine D_2 receptor density remains constant in treated Parkinson's disease. Ann Neurol 1986; 19: 487-492.
20. Bokobza B, Ruberg M, Scatton B, et al. [^{3}H] spiperone binding, dopamine and HVA concentrations in Parkinson's disease and Supranuclear Palsy. Eur J Pharmacol 1984; 99: 167-175.
21. Baron JC, Maziere B, Loc'h C, et al. Loss of striatal [^{76}Br] bromospiperone binding sites demonstrated by positron tomography in progressive Supranuclear Palsy. J Cereb Blood Flow Metab 1986; 6: 131-136.
22. Quik M, Spokes E, MacKay A, et al. Alterations in ^{3}H-spiperone binding in human caudate nucleus, substantia nigra and frontal cortex in the Shy-Drager Syndrome and Parkinson's disease. J Neurol Sci 1979; 43: 429-437.
23. Cross A, Rossor M. Dopamine D-1 and D-2 receptors in Huntington's disease. Eur J Pharmacol 1983; 88: 223-229.
24. Seeman P, Ulpian C, Bergeron C, et al. Bimodal distribution of dopamine receptor densities in brains of schizophrenics. Science 1984: 728-731.
25. Porceddu ML, Giorg O, Orgini E, et al. ^{3}H-SCH 23390 binding sites in the rat substantia nigra: evidence for a presynaptic localization and inervation by dopamine. Life Sci 1986; 39: 321-329.
26. Raisman R, Cash R, Ruberg M, et al. Binding of [^{3}H]-SCH 23390 to D-1 receptors in the putamen of control and parkinsonian subjects. Eur J Pharm 1985; 113: 467-468.
27. Penney JB, Pan HS, Young AB, et al. Quantitative autoradiography of [^{3}H] muscimol binding in rat brain. Science 1981; 214: 1036-1038.
28. Lloyd KG, Shemen L, Hornykiewicz O. Distribution of high affinity sodium-independent [^{3}H]-gamma-aminobutyric acid ([^{3}H]-GABA) binding in the human brain: alterations in Parkinson's disease. Brain Res 1977; 127: 269-278.
29. Walker FO, Young AB, Penney JB, et al. Benzodiazepine and GABA receptors in early Huntington's disease. Neurology 1984; 34: 1237-1240.
30. Van Ness BC, Walkers AE, Bergman MO, et al. Gamma-aminobutyric acid receptors in normal brain and Huntington's disease. Neurology 1982; 32: 63-68.
31. Whitehouse PJ, Trifiletti RR, Jones BE, et al. Neurotransmitter receptor alterations in Huntington's disease: autoradiographic and homogenate studies with special reference to benzodiazepine receptor complexes. Ann Neurol 1985; 18: 202-210.
32. Rinne UK, Koskinen V, Laaksonen, et al. GABA receptor binding in the Parkinsonian brain. Life Sci 1978; 22: 2225-2228.
33. Lo MMS, Niehoff DL, Kuhar MJ, et al. Differential localization of type I and type II benzodiazepine binding sites in substantia nigra. Nature 1983; 306: 57-60.
34. Samson Y, Hantraye P, Baron JC, et al. Kinetics and displacement of [^{11}C] R015-1788, a benzodiazepine antagonist, studied in human brain *in vivo* by positron tomography. Eur J Pharmacol 1985; 110: 247-251.
35. Corda MG, Concas A, Porceddu ML, et al. Striato-nigral denervation increases type II benzodiazepine receptors in the substantia nigra of the rat. Neuropharm 1986; 25: 59-62.
36. Starr MS. Multiple opiate receptors may be involved in suppressing gama aminobutyrate release in substantia nigra. Life Sci 1985; 37: 2249-2255.
37. Abou-Khalil B, Young AB, Penney B. Evidence for the presynaptic localization of opiate binding sites on striatal efferent fibres. Brain Res 1984; 323: 21-29.
38. Moskowitz AS, Goodman RR. Light microscopic autoradiographic localization of mu and lambda opioid binding sites in the mouse central nervous system. J Neurosci 1984; 4: 1331-1342.
39. Garnder EL, Zukin RS, Makman MH. Modulation of opiate receptor binding in striatum and amygdala by selective mesencephalic lesions. Brain Res 1980; 194: 232-239.
40. Reisine TD, Rossor M, Spokes E, et al. Alterations in brain opiate receptors in Parkinson's disease. Brain Res 1979; 173: 378-382.
41. Birdsall NJM, Hulme EC. Muscarinic receptor subclasses. TIPS 1983: 459-463.

42. Calne DB, Stoessl AJ. Transmitter receptor alterations in Parkinson's disease. *In*: Bergmann KJ, Yahr M, eds. Parkinson's Disease. New York: Raven Press 1986 (in press).
43. Foster AC, Fagg GE. Acidic amino acid binding sites in mammalian neuronoal membranes: their characteristics and relationship to synaptic receptors. Brain Res Reviews 1984; 7: 103-164.
44. Herrling PL. Pharmacology of the corticocaudate excitatory postsynaptic potential in the cat: evidence for its mediation by quisqualate or kainate receptors. Neurosci 1985; 14: 417-426.
45. Greenamyre JT, Penney JB, Young AB, et al. Alterations in L-glutamate binding in Alzheimer's and Huntington's diseases. Science 1985; 227: 1496-1499.
46. de Montis G, Beaumont K, Javoy-Agid F, et al. Glycine receptors in the human substantia nigra as defined by [^{3}H] strychnine binding. J Neurochem 1982; 38: 718-724.
47. Sadoul JL, Checher F, Kitabgi P, et al. Loss of high affinity neurotensin receptors in substantia nigra from parkinsonian subjects. Biochem Biophys Res Commun 1984; 125: 395-404.
48. Tran VT, Uhl GR, Perry DC, et al. Autoradiographic localization of somatostatin receptors in rat brain. Eur J Pharmacol 1984; 101: 307-309.
49. Beal MF, Tran VT, Mazurek MF, et al. Somatostatin binding sites in human and monkey brain: localization and characterization. J Neurochem 1986; 46: 359-365.
50. Strittmatter SM, Lo MMS, Javitch JA, et al. Autoradiographic visualization of angiotensin converting enzyme in rat brain with [^{3}H] captopril: localization to a striatonigral pathway. Proc Natl Acad Sci USA 1984; 81: 1599-1603.
51. Quirion R, Shults CW, Moody TW, et al. Autoradiographic distribution of substance P receptors in rat central nervous system. Nature 1983; 303:714-716.
52. Hays SE, Goodwin FK, Paul SM. Cholecystokinin receptors are decreased in basal ganglia and cerebral cortex of Huntington's disease. Brain Res 1981; 225: 452-456.