Neuroreceptor Imaging in Movement Disorders

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Introduction on Movement Disorders

The basal ganglia serve as a major input to the pyramidal tract motor system. The long used term "extrapyramidal" is synonymous with the basal ganglia system. Extrapyramidal disorders are associated with abnormalities of the basal ganglia and are characteristically manifested by a combination of abnormal involuntary movements, alterations in muscle tone, and disturbances in postural stability. Included in this ctegory are the syndromes of parkinsonism, chorea, tremor, athetosis, dystonia, and hemiballism, collectively referred to as *movement disorders*. It also encompasses the syndromes of myoclonus and tics, that probably are caused by lesion sites other than basal ganglia. In general, diagnosis of the particular abnormal involuntary movement depends more on careful clinical obserbation than on laboratory study. Nuclei of the basal ganglia are situated deep in the brain and are difficult to examine. However, recent advancement of radiotracer technologies make it possible to measure the biochemistry and physiology of the basal ganglia.

The basal ganglia comprise five paired nuclei: caudate nucleus, putamen, globus pallidus, substantia nigra, and subthalamic nucleus. The first three lie deep in the cerebral hemispheres and collectively referred as corpus striatum. The subthalamic nucleus lie in the diencephalon, and the substantia nigra is located in the midbrain. Although separated by the internal capsule, the caudate and putamen are similar histologically, chemically, and physiologically, and are considered collectively as *neostriatum* or *striatum*. The striatum serves as the main site of neural input into the basal ganglia, receiving afferents from all parts of the cerebral cortex and thalamus. The striatum interacts mainly with pallidus and substantia nigra back and forth with efferents and afferents neural messages. The pallidus and substantia nigra are also separated by the internal capsules, but are similar microscopically, chemically, and physiologically. These two serve as the major site of neural output from the basal ganglia, with the principal neural pathway going to the thalamus and thense to the premotor cortex. The premotor cortex is one source of the corticospinal (pyramidal) tract, the major cortical efferent pathway controlling motor function.

The substantia nigra modulate the neostriatum by receiving afferents from, and sending efferents back to it. In an analogous fashion, the subthalamic nucleus can be considered to function as a modulator of the pallidus and probably regulates the basal ganglia output to the thalamus. The nigrostriatal pathway contains dopamine and may inhibit the striatum. The other inputs to the striatum, thalamostriatal and glutamate-containing corticostriatal pathways, are excitatory. The GABA-containing efferents from the striatum to the pallidum and substantia nigra are inhibitory. Lesions of the substantia nigra with resulting loss of dopamine in the striatum result in the bradykinetic syndrome of parkinsonism. Drugs that deplete dopamine (reserpine), and drugs that

block striatal dopamine receptors (phenothiazine) can also cause parkinsonism. By contrast, excessive dopamine activity (levodopa overdose) produces the hyperkinetic state of chorea. A lesion of the subthalamic nucleus produces contralateral hemiballism (disinhibition). Lesions in the corpus striatum produce inconsistent patterns of dyskinesias, depending on sites and mode of involvement. Trauma and vascular lesions of striatum can cause athetosis and dystonia, whereas chorea accompanies degenerative loss of neurons in striatum (Huntingtons).

Neuroreceptor Imaging Modalities

Planar brain scan perhaps has no place in neuroreceptor imaging since it deals with deep seated, relatively small functional regions or units. Positron emission tomography(PET) is the most ideal mode as it has superior spatial resolution as well as capabilities of quantitation and attenuation correction. Most of all, PET has powerful advantage of abundantly variable positron tracers. PET has been utilized in this field since early '80s but its availablity is severely restricted due to the high cost. During the past few years, the remarkable advancement in multidetector SPECT cameras along with development of excellent quality SPECT tracers has opened a "new era of brain SPECT" and it is spreading widely throghout the world.

Radiopharmaceuticals of Nigrostriatal Dopamine Pathway

Genral neuronal activity within the basal ganglia can be assessed by PET using F-18-flourodeoxyglucose(FDG), O-15, and O-15-water, but more specific chemical assessment is possible by neuroreceptor binding tracers for both PET and SPECT. Since its first suggestion by Eckelman et al[1] as a potential radiopharmaceuticals in 1979, receptor binding radiopharmaceuticals, particularly as central nervous system receptor imaging agents, have made significant progress. The nigrostriatal pathway extends from the pars compacta of the substantia nigra to the caudate and putamen nuclei of the striatum. The dopaminergic neuron synthesizes dopamine at the nerve terminal. In response to the propagation of axonal action potentials, dopamine is released from vesicles of the nerve terminal into the synaptic cleft. The dopamine that is not bound by postsynaptic dopamine receptors is taken up back into the presynaptic nerve terminal for storage in vesicles. The reuptake process can be examined with several radiotrcers. Included are C-11-nomofensine and C-11-WIN 35,428 for PET, and I-123-β-CIT and I-123-IPT for SPECT.

A large number of PET and SPECT receptor imaging agents have been developed. Most of the earlier works of receptor imaging were done with PET system[2, 3]. With recent advancement of SPECT technology and development of new SPECT receptor agents, SPECT receptor imaging is rapidly growing and will replicate many of the PET studies[4, 5, 7, 8]. Among these radiopharmaceuticals, dopamine receptor imaging agents have been most extensively studied[4, 6, 10-12]. The dopaminergic system is important for human daily function and it is the primary action site for antiparkinsonian agents. Dopamine receptors can be divided into several subtypes, D1-D5, on the basis of genes that characerizes the coupling to adenylate cyclase activity and the differences of the action mechanism of agonists and antagonists[6]. D2 and D1 receptors are most extensively studied and multiple ligands have been synthesized for them[13].

Clinical Applications

Many movement disorders, such as Parkinson's disease (PD), MPTP Toxicity, neuroacanthosis, multiple system atrophy, progressive supranuclear palsy, Huntington's chorea, tardive dyskinesia, Gilles de la Tourette syndrome, Wilson's disease involve changes to dopamine receptor density in the brain. Therefore the dopamine receptor imaging with PET and SPECT in conjunction with appropriate radiopharmaceuticals provides a useful noninvasive tool in the evaluation of these various neurological disorders.

I shall discuss briefly on dopaminergic receptor imaging in PD which has been most extensively studied. In PD, uptake of F-18-flourodopa in the striatum is reduced, more so in the putamen[10, 14]. Similar findings were observed in MPTP toxicity[15, 16]. F-18 fluorodopa PET has been useful in the evaluation of human neurotransplantation of fetal dopamine neurons in PD[17]. It can also provide an index of the number of the functioning nigrostriatal dopaminergic neurons[16]. In patients with untreated PD, an increase in specific binding of C-11-raclopride, a D2 antagonist, is noted[18, 19].

I-123 IBZM SPECT has recently been utilized in D2 receptor imaging in PD and Wilson's disease. A number of I-123 labeled dopamine receptor agents such as IBF, β-CIT, IPT are under the clinical trials[20-23] and they appear to be highly promising SPECT agents. IPT crosses the blood brain barrier easily and selectively binds the dopamine reuptake transporter. Its uptake in the brain is relatively fast and produces very high caudate to occipital ratios. IPT's highly advantageous imaging characteristics may make it the radiopharmaceutical of choice for the studies of the transporter.

PET will continue to play important role in neuroreceptor imaging, while SPECT receptor imaging will replicate many of PET roles in the diagnosis of movement disorders.

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