# PET/SPECT Assessment of the Dopaminergic System in Health and Disease

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More is known about the dopaminergic system than almost any other neurotransmission process. This knowledge has led to improvements in patient care. Over two decades ago, dopamine was found to be deficient in Parkinson's disease, a finding which led eventually to the treatment of the disease by the administration of the dopamine precursor, L-DOPA. Neurons secreting dopamine as a neurotransmitter lie in the substantia nigra with axons extending to the caudate nucleus and putamen (the nigrostriatal pathway)[14], or in the limbic cortex, including the amygdaloid nuclei, hippocampus, anteromedial frontal cortex, and the medial and lateral habenula (the mesolimbic pathway)[12]. D2 dopamine receptors are also believed to be located primarily on instrinsic interneurons within the caudate and putamen[18]. Another type of dopamine receptor (the D1 receptor) differs from the D2 type in that it is involved in that conversion of ATP to cyclic AMP.

The direct action of dopamine on neurons is inhibitory. Administration of apomorphine, a direct dopamine receptor agonist, reduces the firing rate of dopaminergic neurons. Dopamine may inhibit neuronal activity by direct action, but can indirectly produce a positive response by inhibiting inhibitory neurons. The activation of post-synaptic neurons is the result of the interactions of multiple neurotransmitters and neuroreceptors, some stimulatory and others inhibitory, with the receptors serving as recognition sites to increase the specific responses to incoming pre-synaptic information. Second and third "messengers" subsequently transduce the information to effect the process of neurotransmission in post-synaptic neurons.

In Parkinson's disease, the dopaminergic system modulates the neuronal servomechanisms that control motion. Administration of L-DOPA increases dopamine synthesis and synaptic dopamine concentrations, and thereby activates post-synaptic receptors, some of which may be inhibitory. Dopamine receptor agonists, such as bromocryptine, have similar effects. Modulatory control of movement by increases in dopamine synthesis improves patients with Parkinson's disease, who are characterized by exceedingly low dopamine concentrations in the caudate nucleus and putamen as a result of degeneration of the dopaminergic neurons in the substatia nigra[1]. Thus, Parkinson's disease can be thought of as a dopamine deficiency disease.

## SCHIZOPHRENIA

In the 1950's it was found that drugs that block D2 dopamine receptors improve patients suffering from schizophrenia. These observations raised the possibility that the dopaminiergic neuronal system might be involved. Symptoms such as excitement, restlessness, irritability, aggressiveness, and insomnia are the first to be diminished by neuroleptic drugs that block D2 dopamine receptors. Affective symptoms, such as anxiety, depression and social withdrawal respond next, with symptoms related to

perception and cognition, such as delusions, hallucinations and thought disorders, disappearing only after 6~8 weeks of receptor blockade.

Carlsson of the University of Goteborg in Sweden first proposed that abnormalities of the neurotransmission system involving dopamine might be involved in schizophrenia[5]. He recoginzed that drugs that help schizophrenic patients block D2 dopamine receptors, and that amphetamines, which elevate synaptic dopamine concentrations, exacerbate symptoms in schizophrenic patients and produce psychotic states resembling schizophrenia in otherwise normal persons. Several post-mortem studies of the brains of some schizophrenic patients have indicated that D2 dopamine receptor densities are increased in the caudate nucleus and putamen. In psychotic patients, inhibiting D2 dopamine receptors with neuroleptic drugs, such as haloperidol, decreases hallucinations, delusions and thought disorder[4,17]. In some patients with schizophrenia, dopamine receptor blocking drugs, in addition to their anti-psychotic effects, by inhibiting the activity of the dopaminergic system, diminish movement, and can cause rigidity and tremor, a syndrome called "tardive dyskinesia."

## IMAGING DOPAMINE RECEPTORS

In 1978, Kuhar et al demonstrated the feasibility of using autoradiography to image D2 dopamine receptors in rats[13]. In 1983, N-methyl spiperone (NMSP), labeled with carbon-11 made it possible to carry out the first successful imaging of neuroreceptors in the brain of aliving human being[19]. Most of the D2 dopamine receptors in human beings were found in the caudate nucleus and putamen. The receptor binding of the tracer in these regions was found to decrease dramatically between the ages of 19 and 73 years, with most of the decrease occurring before the ago of 40[20]. Prior administration of neuroleptic drugs that block dopamine receptors were observed to inhibit the uptake of the tracer by the receptors. From studies in which receptor binding of the tracer was examined in the control state, and after the adminstration of the receptor-inhibiting drug, haloperidol, it was possible to calculate receptor density and affinity in various brain regions, and to express the results in units of picomoles/gram[21,22].

In the first studies of D2 dopamine receptros with 3-N-[11 C] methylspiperone ([11 C] NMSP), the ratio of the tracer activity in the caudate nucleus and putamen to that in the cerebellum was found to increase as a linear function of time after intravenous injection of the tracer for at least 120 minutes. The slope of the line relating the ratio of counts in the caudate and putamen to the count rate in the cerebellum decreased markedly after the administration of dopamine-receptor inhibiting drugs, such as haloperidol. This slope also decreased with the increasing age of normal persons[20]. The slope of the caudate/cerebellar ratio as a function of time after injection of the high specific activity tracer dose reflected normal or decreased availability of the receptors, but was not sensitive to an increase in receptor availability, because, in such cases, the accumulation of the tracer was limited by blood flow delivering the tracer to the regions, rather than receptor density and affinity. Thus, the caudate/cerebellar ratio at 45 minutes after injection of the tracer, or the slope of the line relating the ratio to time after injection could be used an index of receptor availability, but preliminary studies of schizophrenic patients, using the high specific activity tracer, failed to reveal any differences between schizophrenic patients and normal persons. This was because the accumulation of the tracer in both patients and normal persons was determined by blood flow, so that no further increase in receptor density was detectable in schizophrenic patients. However, administration of haloperidol revealed differences between schizophrenic patients and normal persons. After inhibition of the receptors by

haloperidol, more receptors remained available in the schizophrenic patients than in the age-matched normal controls. The performance of two studies—one in a control state and another after receptor inhibition with haloperidol, revealed that many schizophrenic patients had receptor densities that were greater than age-matched normal persons[23]. Because D2 dopamine receptor density falls dramatically with age, it was necessary to compare the patients to age-matched controls. When about 50% of the receptors had been blocked by haloperidol, the amount of the radioligand C-11 N-methyl spiperone accumulated by the caudate and putamen was a function of the receptor density and affinity, rather than primarily a reflection of blood flow. With the receptors unblocked, the high specific activity tracer dose was able to detect decreased but not increased receptor density.

In the case of irreversibly-bound ligands, such as carbon-11 methyl spiperone, kinetic modeling must include measurement of the rate of entry of the tracer into the receptor-rich region (the "input function"). One must be able to separate measurements of the rate of delivery of the receptor to a region from the rate of binding of the ligand to the receptor. This distinction is necessary in order to calculate receptor density (Bmax) and affinity (Kd). The rate constants of binding of the tracer to the D2 receptor in both the unblocked and blocked states are calculated from the time course of brain radioactivity in the regions of interest, together with the measurements of the time course of plasma radioactivity.

## ASSESSING DOPAMINERGIC NEUROTRANSMISSION

Assessment of the status of dopaminergic neurons could provide a biological marker for certain types of mental dysfunction. A reasonable hypothesis is that increased dopaminergic "tone" can result in impaired inhibition of pre-synaptic stimuli and deficient "filtering" of exteroceptive, proprioceptive and enteroceptive neuronal activity. Some patients with schizophrenia have normal concentrations of D2 dopamine receptors, while others have elevated concentrations. Thus, diagnostic categories, such as schizophrenia, are likely to be chemically heterogeneous.

It is not known whether increased synaptic dopamine concentrations (which have recently been described by Wong et al from our laboratory), or increases in D2 dopamine receptors precede or follow the development of symptoms of schizophrenia. Probably, both pre-synaptic and post-synaptic dopaminergic neurons are hyperactive. Elevated D2 dopamine receptors are not found only in patients with schizophrenia, but are elevated in patients with psychotic depression and Tourette's syndrome[25].

## MONITORING DRUG TREATMENT

Many drugs act by stimulating or blocking receptors. Drugs that block dopamine receptors diminish delusions and hallucinations in psychotic patients, and improve cognitive function. Other druge that act by inhibiting neuroreceptors are: cimetidine, which blocks histamine receptors; propranolol which blocks beta adrenergic receptors; and haloperidol which blocks dopamine receptors. The widely used drug valium stimulates benzodiazepine receptors, producing an inhibitory effect on neurotransmission, which accounts for its tranquilizing effects. Dopamine receptors can change their internal molecular structure in a manner which alters their functions, at times even switching from an excitatory to an inhibitory functional state. The effects of neuroleptic drugs in blocking dopamine receptors can be assessed in experimental animals and human beings by simplified detector systems, as well as by more complex PET imaging.

## SPECT RADIOLIGANDS FOR THE STUDY OF THE DOPAMINERGIC SYSTEM

Recently, both carbon-11 and iodine-123 compounds have been developed for the study of the site of dopamine re-uptake on pre-synaptic neurons. This provides a third type of biological marker, in addition to measurement of dopamine synthesis, and the status of post-synaptic neurons. It is likely that increases in knowledge of the dopaminergic system will be rapid in the next few years.

## REFERENCES


1) Arnt J: *Behavioral studies of dopamine receptors: Evidence for regional selectivity and receptor multiplicity. In: dopamine Receptors, edited by I. Creese and CM Fraser, pp 199-231, Alan R. Liss, Inc, NY, 1987*
2) Breese GR, Baumeister AA, McCown TJ, Emerick SG, Frye GD, Mueller RA: *1984a, Neonatal-6-hydroxydopamine: Model of susceptibility for self-mutilation in the Lesch-Nyhan Syndrome. Pharmacol Biochem Behav 21:459-461, 1984a*
3) Breese GR, Baumeister AA, McCown TJ, Emerick SG, Frye GD, Crotty K, Mueller RA: *Behavioral differences between neonatal and adult-6-hydroxydopamine-treated rats to dopamine agonists: Relevance to neurological symptoms in clinical syndromes with reduced brain dopamine. J Pharmacol Exp Ther 321:343-354, 1984b*
4) Canonico PL, Valdenegro CA, MacLeod RM: *The inhibition of phosphotidylinositol turnover: A possible post receptor mechanism for the prolactin secretion-inhibiting effect of dopamine. Endocrinology 113:7-14, 1983*
5) Carlsson A: *Antipsychotic drugs, neurotransmitters, and schizophrenia. Am J Psychiatr 135:165-173, 1978*
6) Crow TJ, Cross AJ, Johnstone EC, Owen F: *Two syndromes in schizophrenia and their pathogenesis. In: Schizophrenia as a brain disease, edited by FA Henn and HA Nasrallah, pp 196-234. Oxford University Press, NY, 1982*
7) Eriksson L, Farde L, Blomquist G: *Kinetic analysis of 11C-raclopride binding to central D2-dopamine receptors. J Nuc Med 29(5):820, 1988*
8) Farde L, Wiesel F-A, Hall H, Halldin C, Stone-Elander S, Sedvall G: *No D2 receptor increase in PET study of schizophrenia. Arch Gen Psychiatry 44:671, 1987*
9) Garnett RS, Firnau G, Nahmias C: *Dopamine visualized in the basal ganglia of living man. Nature 305: 137-138, 1983*
10) Goldstein M, Kuga S: *Dopamine (DA) agonist induced compulsive biting (CB) behavior in monkeys: animal model for Lesch-Nyhan syndrome. Soc Neurosci 10:239.1, 1984. (abs)*
11) Goldstein M, Kugs S, Kusano N, et al: *Dopamine agonist induced self-mutilative biting behavior in monkeys with unilateral ventromedial tegmental lesions of the brain stem: Possible pharmacological model for Lesch-Nyhan syndrome. Brain Res 1985*
12) Joyce JN, Lexow N, Bird e, Winodur A: *Organization of dopamine D1 and D2 receptors in human striatum: Receptor autoradiographic studies in Huntington's disease and schizophrenia. Synapse 2(5):546-556, 1988*
13) Kuhar MJ, Murrin LC, Malouf AT, Klemm N: *Dopamine receptor binding in vivo: The feasibility of autoradiographic studies. Life Sci 22:203-210, 1978*
14) Schwarcz R, Creese, I Coyle JT, Snyder SH: *Dopamine receptors localized on cerebral cortical afferents to rat cortical afferents to rat corpus striatum. Nature 271:766-768, 1978*
15) Sedvall G, Farde L, Hall H, Wiesel F: *Application of the PET scan to the study of schizophrenia in Schizophrenia: The major issues, Heinemann Medical Books Oxford, 1988*
16) Seeman P, Bzowej NH, Guan H-C, Bergeron C, Becker LE, Reynolds GP, Bird ED, Ridderer P, Jellinger K, Watanabe S, Tourtellotte WW: *Human brain dopamine receptors in children and aging adults. Synapse 1:399-404, 1987*
17) Simmonds SH, Strange PG: *Inhibition of inositol phospholipid breakdown by D2 dopamine receptors in dissociated bovine anterior pituitary cells. Neurosci Lett 60:267-272, 1985*
18) Trugman JM, Geary W, Wooten GF: *Localization of D2 dopamine receptors to intrinsic striatal neurones*

*by quantitiative autoradiography. Nature 323:267-269, 1986*

19) Wagener HN, Burns HD, Dannals RF, et al: *Imaging dopamine receptors in the human brain by positron tomography. Science 221:1264-6, 1983*

20) Wong DF, Wagner HN Jr, Dannals RF, et al: *Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. Science 226:1393-1396, 1984*

21) Wong DF, Gjedde A, Wagner HN Jr: *Quantification of neuroreceptors in the living human brain. Part I. Association rate of irreversibly bound ligands. J Cereb Blood Flow and Metab 6:137-146, 1986a*

22) Wong DF, Gjedde A, Wagner HN Jr, et al: *Quantification of neuroreceptors in the living human brain. Part II. Assessment of receptor density and affinity using inhibiton studies. J Cereb Blood Flow and Metab 6:147-153, 1986b*

23) Wong DF, Wagner HN Jr, Tune Le, et al: *Positron emission tomography reveals elevated D2 dopamine receptors in drug-naive schizophrenics. Science 234: 1558-1563, 1986d*

24) Wong DF, Young D, Young LT, Tune LE, Minkin E, Chan B, Midha K, Dannals RF, Parker RD, Wilson PD, Wilson AA, Ravertrrr HT, Natarajan TK, Wagner HN Jr, Gjedde A: *Validation studies of PET D2 dopamine receptor quantification in schizophrenia using [C-11] NMSP. J Nuc Med 30(5):731, 1989a*

25) Wong DF, Young LT, Pearlson G, Singer H, Tune L, Ross C, Dannals RF, Wilson AA, Ravert HT, Links J, Wagner HN Jr, Gjedde A: *D2 dopamine receptor densities measured by PET are elevated in several neuropsychiatric disorers. J Nuc Med 30(5): 731, 1989b*