

Dopamine imaging markers and predictive mathematical models for progressive degeneration in Parkinson's disease

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Summary – We conducted PET imaging studies of modulation of dopamine transporter function and MRS studies of neurochemicals in idiopathic primate Parkinson's disease (PD) model induced by long-term, low-dose administration of MPTP. MR spectra showed striking similarities of the control spectrum of the primate and human striatum as well as MPTP-treated primate (six months after cessation of MPTP), and Parkinson's disease patient striatum (68 year old male; Hoehn-Yahr scale II; 510 mg/d L-DOPA). The choline/creatine ratio was similar in the MPTP model and human parkinsonism, suggesting a possible glial abnormality. The progressive degeneration of dopamine re-uptake sites observed in our PD model can be expressed by a time dependent exponential equation $N(t) = N_0 \exp(-(0.072 \pm 0.016) t)$, where N_0 represents intact entities (dopamine re-uptake sites before MPTP) and 0.072 per month is the rate of degeneration. When the signs of PD appear, $N(t)$ is about 0.3–0.4 times N_0 . Interestingly, this biological degenerative phenomena has similar progression to that observed in cell survival theory. According to this theory and calculated degeneration rate, predictive models can be produced for regeneration and protective treatments. © 1999 Elsevier, Paris

dopamine transporters / L-DOPA / MPTP / MRS / Parkinson's disease / PET

Parkinson's disease (PD) is one of the most common neurologic disorders. It is estimated that about 1 million Americans are affected by Parkinson's disease and about 40,000 new patients are diagnosed every year. Hypotheses of the etiology of PD are focused on possible genetic links (such as *α-synuclein*) and on the potential contribution of toxins (exogenous and/or endogenous) [78, 79] and their potential interaction with genetic components [15]. At the cellular level PD is characterized by severe depletion of DA neurons and associated loss of synapses in the basal ganglia.

PD is diagnosed clinically based on the cardinal signs: tremor, rigidity, bradykinesia and postural instability [66]. Improved understanding of the pathophysiologic mechanism underlying parkinsonian signs and symptoms [70], as well as refinement of methods and techniques in neuroradiology, neurosurgery and neurophysiology, have stimulated the recent interest in developing therapeutic techniques. Investigations of MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine)-induced parkinsonism in non-human primates have led to the hypothesis that dopamine deficiency in striatum leads to unbalanced activity from subthalamic nucleus into globus pallidus, resulting excessive inhibitory out-

flow (increased and synchronized spontaneous firing rate) from the internal segment of the globus pallidus [25]. This suppresses the motor thalamus which reduces activation of the cerebral cortex motor system, resulting in deficiency of movement [6, 25]. To interrupt this basal ganglia-motor system circuitry; three different therapeutic modalities are used, namely pharmacological therapy [52, 72, 80], fetal cell transplantation [28, 29, 51, 59], and surgical procedures such as pallidotomy [30, 36], thalamotomy [46] and chronic thalamic high frequency stimulation [4].

A recent extensive PD twin study indicates that physiological and toxic factors play roles in causing typical PD as humans age [79]. This progressive decline of dopamine (DA) terminals seen in idiopathic PD can be closely modeled in the non-human primate *Macaca fascicularis* by a low-dose exposure of the mitochondrial toxin, MPTP [8, 42, 81].

Developing radiopharmaceuticals for detection of dopamine terminals has been a major challenge for pharmacological research. Since autoradiographic studies of using cocaine analogs to label dopamine transporters were introduced [49], tropane derivatives have been widely used in PET imaging studies of

Parkinson's disease and drug abuse [35, 40, 52]. The latest developments, however, involve specific and sensitive cocaine analogs labeled with technetium-99m or iodine-123, used in single photon emission tomography studies of dopaminergic system [7, 22, 38, 53, 64].

The ability to observe both physiology and function in small areas within the brain is now possible with high resolution PET and MR imaging techniques [11, 16, 47]. The potential use of positron emission tomography (PET) as a research tool in movement disorders has been demonstrated in studies of brain dopamine function [74] and glucose metabolism associated with movement disorders [1, 43, 71]. Recently, high resolution PET imaging has been widely used in studies with animal models of Parkinson's disease [8-10, 18, 19, 42, 48, 81]. In addition, advances in receptor studies [10, 32, 42], and magnetic resonance spectroscopy of neurodegeneration [8, 24, 39, 44, 47], provide specific functional neurochemical information.

Our earlier work indicated; (1) that a stable Parkinson-like disease appears after chronic administration of a neurotoxin, MPTP; (2) that progressive dopaminergic fiber loss can be detected by positron emission tomography (PET) using carbon-11 labeled 2 β -carbomethoxy-3 β -(4-fluorophenyl) tropane (¹¹C-WIN 35,428 or ¹¹C-CFT) to label dopamine reuptake sites [42, 81]; and, (3) that progressive physiological changes of neurochemicals occur as observed with MRS and PET [8]. In the present article, we compare imaging characteristics of ¹¹C-CFT with those of ¹⁸F-L-6-fluorodopa, and show that by using ¹¹C-CFT the progressive degeneration of dopamine terminals can be mathematically modeled to determine the rate of degeneration and predict the time of onset of PD signs.

MATERIALS AND METHODS

Study design

Longitudinal PET and MRS imaging studies were carried out in six MPTP-treated primates (*Macaca fascicularis*) to follow the progression of the MPTP-induced degeneration. These primates served as their own controls in studies prior MPTP. Control studies with MRS included four additional primates (table 1). Comparison of MRS primate data was done with one Parkinson's disease patient (68 year old male; Hoehn-Yarn scale II, 510 mg/d L-DOPA) and an aged matched normal volunteer.

MPTP-lesion in primates

A slow neurotoxic lesion of dopaminergic cells located in the substantia nigra and in the ventral tegmental area was

Table 1. Striatal neurochemical changes in primates 0.5–2 years after cessation of MPTP treatment.

Metabolite Ratio	Controls (n = 10)	MPTP (n = 6)
NAA/Cr (range)	2.38 ± 0.11 (2.3–2.5)	2.09 ± 0.29* (1.7–2.5)
Cho/Cr (range)	0.83 ± 0.06 (0.8–0.9)	1.20 ± 0.15*** (1.0–1.4)

Unpaired Student's t test values for difference from control: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

obtained by repetitive administration of MPTP dissolved in saline and immediately administered intravenously to primates (0.6 mg/kg i.v., every two weeks until behavioral stability) under light anesthesia (ketamine, 5 mg/kg i.m.), as previously described [81].

In this chronic model, behavioral signs developed gradually over 9–14 months, progressing from bradykinesia to akinesia in all limbs. Tremor also occurred as the last PD sign. These signs did not spontaneously recover, in contrast to acutely induced MPTP-PD models [20, 31, 54].

PET imaging studies of dopamine transporters

Instrumentation

Positron emission tomography studies were carried out with PET scanning system, PCR-I [11], as earlier described [8].

Labeling of radiopharmaceuticals

Radiolabeling of ¹¹C-CFT was published earlier [10] and L-6-¹⁸F-fluorodopa was prepared according to the fluorodemercuration method [62].

Experimental procedures

For PET imaging, animals were anaesthetized with ketamine/xylazine (30/3 mg/kg i.m.) initial dose and anesthesia was maintained with half a dose hourly injections as needed. Catheterization of the femoral artery and vein was used for collection of blood samples and injection of labeled ligand. The animal was placed in the imaging position, and the head was adjusted into a stereotactic headholder with the earbar at the origin. Interior orbital supports ensure that images were acquired in pseudocoronal plane perpendicular to the orbito-meatal line. This allows superposition of data from MRI and MRS studies. After the injection of labeled ligand, ¹¹C-CFT or ¹⁸F-L-6-fluorodopa (5mCi, specific activity 600–1,000 mCi/ μ mol) into the femoral vein, imaging data were collected stepwise on seven levels (A30 (30 mm anterior from the origin), A25, A20, A15, A10, P5 (5 mm posterior from the origin) and P10) initially using 15 s frames. The frame time was subsequently increased to

60 s, the total imaging time being 90 min for ^{11}C -CFT and 120 min for ^{18}F -L-6-fluorodopa. While imaging with ^{11}C -CFT, 18 arterial blood samples of 0.1 mL were collected at different time points starting from 10 s frequency and ending with 15 min frequency to monitor the decrease in radioactivity. In addition three arterial blood samples were collected for HPLC analyses of metabolites of labeled ligand.

Calibration of the positron tomograph was performed in each study session using a cylindrical plastic phantom (diameter 6 cm) and ^{18}F -solution. Cross calibration with a gamma counter (Packard Cobra Auto-gamma, Downers Grove, IL, USA) was carried out using the same solution. Imaging data were corrected for uniformity, sensitivity, attenuation, decay and collection time. PET images were reconstructed using Hanning weighted convolution back-projection [13]. Regions of interest including left and right caudate and putamen, frontal, parietal and temporal cortex, thalamus and cerebellum were drawn on each level and activity per unit volume, percent activity of injected dose, and ligand concentration were calculated. Plasma data were corrected for counting efficiency, calibration factor and measured metabolites of ^{11}C -CFT and percent activity of injected dose and ligand concentration were calculated. Plasma data was used as an input function in the kinetic modeling.

Receptor studies with ^{11}C -labeled CFT

The kinetic behavior of ^{11}C -CFT was studied with a three compartmental model approach [77]. In the three compartmental model, the first compartment is the plasma pool, the second is the exchangeable tracer pool including free and nonspecifically bound ligand in the brain, and the third compartment is a trapped tracer pool including bound ligand in the brain. The exchangeable tracer pool contains ligand but no receptors and the third compartment includes all the receptors, partly or totally occupied by ligands. The kinetic parameters k_3 and k_4 describe the binding to and dissociation from receptors.

The transfer coefficients k_1 – k_4 were mathematically resolved using the SAAM II program [26]. For stabilization of the k values the fitting procedure was performed using three steps. Since cerebellum does not have specific receptor binding or it is negligible, fitting was done in the cerebellum data letting all the k -values float. Briefly, with estimates for the initial conditions for the k -values, the differential equations were integrated using an adaptable fourth order Runge-Kutta method with suitable accuracy (tolerance 10^{-7}). Iterations continued until sufficient convergence was achieved for the system parameters (k_1 – k_4). The ratio k_1/k_2 was calculated. In further iterations of the striatal data the

fixed ratio (k_1/k_2) was used as a constraint to reach parameter optimization. Regional binding parameters k_3/k_4 were calculated for each study.

Comparison of imaging characteristics of ^{11}C -CFT and ^{18}F -L-6-fluorodopa

Comparison of imaging characteristics of ^{11}C -CFT and ^{18}F -L-6-fluorodopa was based on obtained contrast in striatum compared to cerebellum. The difference of the striatal and cerebral accumulation of radioactivity was fitted into gamma variate function and the maximum value was divided by the value of the cerebral activity at that time point.

Modeling of progressive degeneration

To analyze MPTP-induced progressive degeneration, values of striatal binding potentials of ^{11}C -CFT at different time points during the MPTP-administrations (time = 0 when MPTP-administration was started) were fitted into an exponential function; $N(t) = N_0(t = 0) \exp(-k t)$. N_0 denotes binding potential in the intact dopamine terminals or arbitrary estimate of the intact dopamine terminals, $N(t)$ is the corresponding value after degeneration of time (t) and k is a rate of degeneration.

MRS studies of neurochemicals

For these studies, we utilized single voxel spectroscopy of the basal ganglia. We chose voxels centered in the striatum for both monkeys and PD patients. Voxels were between 0.5–1 cm³ in the monkey brain and between 3–5 cm³ in the human brain. Water suppression was performed using CHESSE pulses and localization by a standard PRESS-type sequence with TR/TE of either 2000/272 or 2000/136 ms. Spectra were processed using the NMR1 program (NMRI, Syracuse, NY), by curve fitting the entire spectrum and integrating the areas of the major metabolites. Integrals were then normalized to the creatine peak at 3.03 ppm (Cr) as a standard.

Metabolite quantification

We found NAA/Cr ratios to be reliable quantitative indicators of neurodegeneration. This reliability was indicated by the large differences noted between the MPTP-lesioned animals. In the case of single voxel spectroscopy we used a fully relaxed non-water suppressed spectrum from the voxel. This provides a constant internal reference for a metabolite/water ratio even if, due to metabolite T1 and T2 errors, absolute concentrations remain elusive. The stan-

standard deviations in this technique were very small, and allowed to make direct inter-animal comparisons.

Characterization of the elevated lipid/lactate peaks were performed using multiple TE values to characterize the coupling constants and double quantum filtration to estimate how much of the intensity is due to lactate. Due to the relatively shorter T1 values of lipids, we used inversion recovery PRESS spectra with variable TI values to characterize the lipid T1s in order to estimate the concentrations. In addition, we have implemented a STEAM sequence with the capability getting TE's down to 6 ms. This enables quantitative measurements of the lipid and macromolecular components when combined with the inversion recovery experiments.

RESULTS

Figure 1 shows ^{11}C -CFT and ^{18}F -L-6-fluorodopa distribution in the same control primate. Sixty minutes before the ^{18}F -L-6-fluorodopa injection the primate was pretreated with carbidopa (5 mg/kg) to reduce peripheral metabolism. These images show the striking specificity of ^{11}C -CFT to image striatal function. The contrast of striatal binding using ^{11}C -CFT was 3.25 ± 0.56 and correspondingly 1.67 ± 0.23 using ^{18}F -L-6-fluorodopa. Striatal data were averaged from putamen data of levels A20 and A15 from the left and right sides and caudate data of levels A25 and A20 from both sides. Figure 2 shows relative ^{11}C -CFT binding distribution before and during MPTP administration in an asymptomatic and symptomatic stage. Three coronal brain

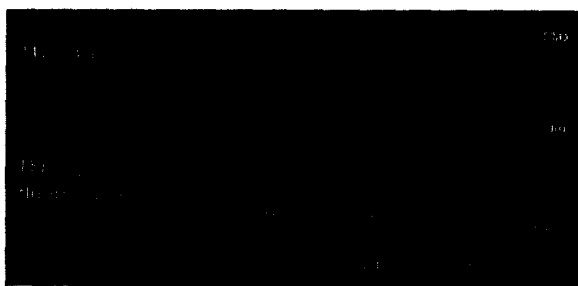


Figure 1. Color coded PET images showing ^{11}C -CFT and ^{18}F -L-6-fluorodopa accumulation in the same control primate brain. Sixty minutes before fluorodopa injection the animal was pretreated with carbidopa (5 mg/kg) to reduce peripheral dopamine metabolism. ^{11}C -CFT images are acquired 60–62 min after injection and ^{18}F -L-6-fluorodopa images 90–120 min after injection. Four images represent the brain levels A25, A20, A15 mm anterior and P5 mm posterior from the reference plain. After corrections for decay, acquisition time and injected activity the highest pixel value of the four ^{11}C -CFT images was normalized to 10,000 and the lowest to 0. All the ^{11}C -CFT images were normalized according to this scale. Correspondingly, after corrections the four ^{18}F -L-6-fluorodopa images were normalized similarly.

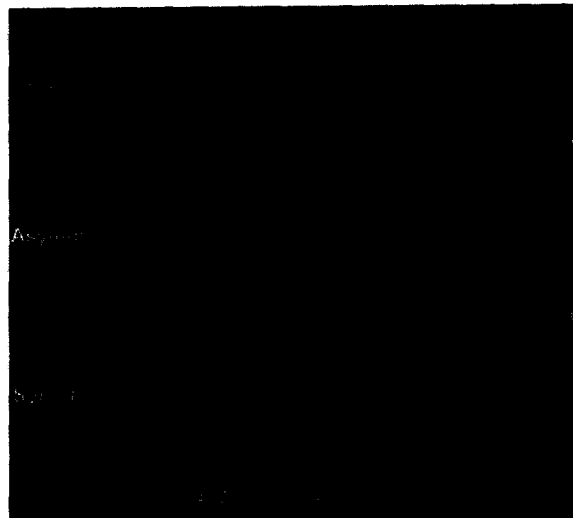


Figure 2. Color coded PET images showing relative ^{11}C -CFT binding in a monkey brain 60–62 min after injection. The three images represent the levels throughout caudate-putamen (A25, A20 A15 mm anterior of the reference plain) before MPTP treatment, after 3 MPTP injections, when the primate was asymptomatic and after 9 months of MPTP treatment, when the monkey was symptomatic. After corrections for decay, acquisition time and injected activity, the average count density was determined in cerebellum study and ^{11}C -CFT images of the three coronal brain levels were divided by this value on the pixel basis individually in each study. Finally, the highest pixel value in the nine images was normalized to 10,000 and the lowest to 0. All the images were normalized according to this scale.

levels (A25, A20 and A15) through the striatum show that degeneration in putamen is more severe than in caudate. The progressive degeneration of dopamine reuptake sites observed in our primate PD model can be expressed by an exponential equation $N(t) = N_0 \exp(-kt)$, where N_0 represents intact entities (dopamine reuptake sites) and k represents the rate of progressive degeneration. Figure 3 shows progressive degeneration observed in six primates during low-dose MPTP administrations. The exponential curve fitted to the calculated binding potential values is $N(t) = N_0 \exp(-(0.072 \pm 0.016)t)$ indicating that the rate of MPTP-induced degeneration is 0.072 per month. When signs of PD appeared, $N(t)$ was about $(0.3-0.4) N_0$.

We have also investigated neurochemical changes with MRS in the same primates as imaged by PET using ^{11}C -CFT. Spectra from a control and typical MPTP-treated primate striatum (six months after cessation of MPTP therapy) is shown in figure 4 with comparison to MR spectra of a parkinsonian patient (68 year old male, Hoehn-Yahr scale II, 510 mg/d L-DOPA) and an age matched control patient. Note the pronounced changes

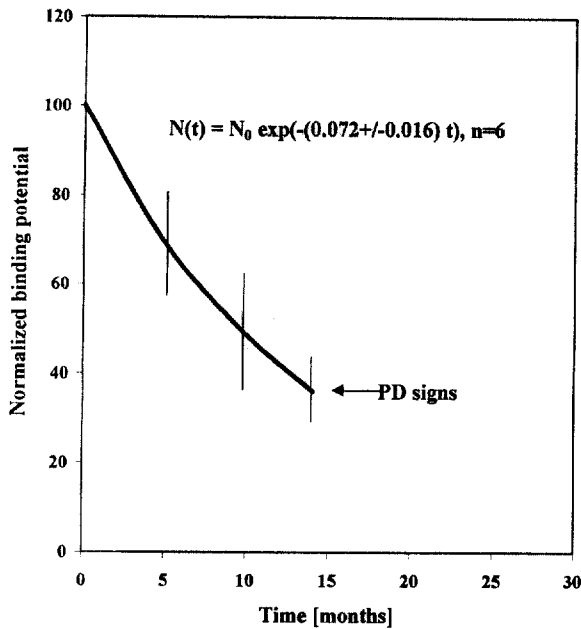


Figure 3. Model for the progressive degeneration and the appearance of parkinsonism in MPTP treated primates. Control value of the binding potential (before MPTP) was normalized individually to 100 and all the other values were normalized according this scale. (Raw data from [8].)

compared to the control striatum. Lactate and/or lipid peaks are visible in both the patient and the primate, but not in the controls. In all the primates studied ($n = 6$), the lactate/lipid peaks had disappeared after an additional eight months [8]. These data indicate an acute metabolic process which resolves after a period of time, and is consistent with the time course for macrophage infiltration. Unfortunately we were unable to collect enough data to completely assay the time course of changes in all the metabolites over time. Future studies will entail collection of more data to determine the complete spectroscopic time profile of evolution of the neurochemical changes.

In the MPTP model there is a significant decrease in NAA, which is larger than that seen in our PD patients (NAA/Cr = 2.09, $n = 6$ vs. 2.33 in PD patients, $n = 23$, B. Jenkins, personal communication). This is significant since our control human population had identical NAA/Cr levels to the primate controls (2.33 ± 0.46 in humans; $n = 20$ vs. 2.38 ± 0.11 in primates, $n = 10$, Jenkins, personal communication). Notably, in the MPTP monkeys there was a large increase in the Cho/Cr ratio, very similar to what is seen in our PD patients (Cho/Cr = 1.2). Choline may be reflective of gliosis as the choline concentration in glial cells is twice that in neurons or of macrophage activity. A quantitative summary of our primate results is shown in the *table I*.

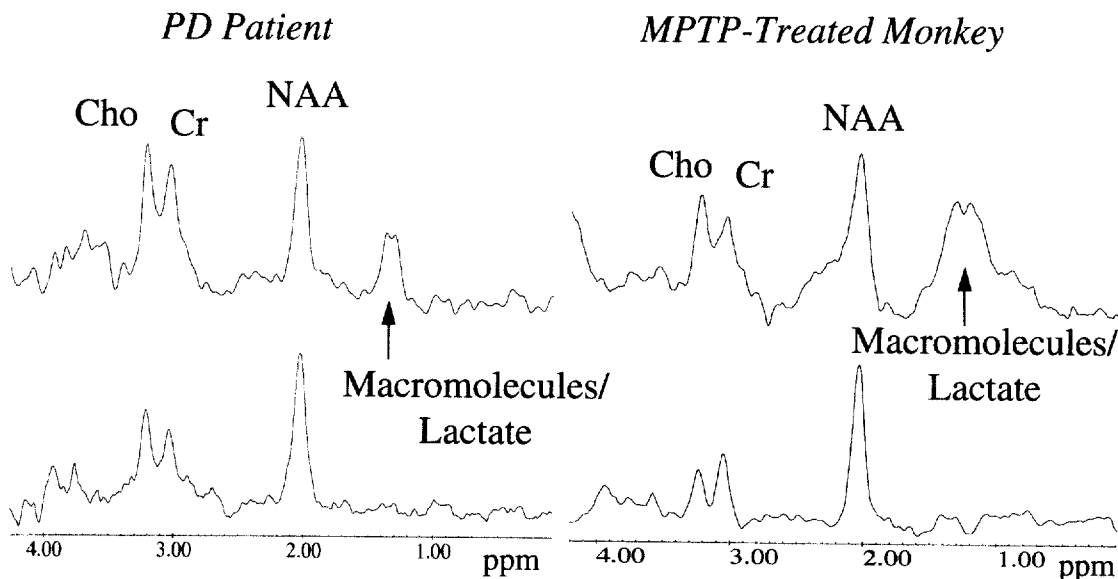


Figure 4. Striatal spectra from: Left) A PD patient (male; 68 years old; Hoehn-Yahr scale II; 510 mg/d L-DOPA), and an age-matched control. Right) An MPTP-treated monkey 6 months after cessation of MPTP-treatment and a control monkey. Major neurochemicals observed are indicated. Note the striking similarity of the control spectrum of the primate and human as well MPTP-treated primate and Parkinson's disease patient (TR/TE 2000/272ms; PRESS).

DISCUSSION

Realistic primate models that mimic the progressive changes of PD are of critical importance for developing neural therapeutic techniques. The optimal procedure for therapy-induced behavioral recovery observed in many clinical and experimental studies is still unclear.

Primate models of parkinsonism were developed using MPTP administered according to different protocols [12, 56]. Stereotaxic application of MPTP (or its active metabolite MPP⁺) in substantia nigra or in the striatum, as well as intra-carotid injections or repeated intravenous administration during 5–10 days [12, 45, 56], generally induces a marked dopamine depletion resulting in a severe akineto-rigid parkinsonian syndrome (often requiring drug therapy) within weeks following treatment. Such studies demonstrated that MPTP-induced behavioral, neurochemical and anatomical changes are analogous but not identical to alterations observed in parkinsonian patients [12, 21]. Acute protocols (toxicity induced over one to five days) of MPTP differ from idiopathic (PD) in several aspects: (1) pathologic changes in idiopathic PD extend beyond the substantia nigra [37]; whereas, the substantia nigra, and to a lesser extent the ventral tegmental area, are the regions primarily lesioned by MPTP toxicity; (2) acute MPTP-administration to non-human primates does not produce an uneven pattern of striatal dopamine loss described in idiopathic PD, with relative sparing of dopamine levels in the caudate nucleus compared to the putamen [21]; (3) acute MPTP toxicity in non-human primates also creates motor symptoms that may recover with time [20, 54]; (4) an acute administration protocol does not reproduce the chronic and slow degeneration of dopamine neurons that occurs in idiopathic PD. Recently, a less acute primate model of various stages of PD has been obtained by unilateral intra carotid infusion [48] combined with sequential systemic doses of MPTP [19]. In addition, a chronic model of PD has been introduced by using daily low dose systemic injections of MPTP for 22 days [5].

Following these principles, our studies involving chronic low-dose administration of MPTP [8], have clearly demonstrated that by repeated administration of the neurotoxin over a long period of time, it is possible to increase the selectivity of the neurotoxin for specific subpopulations of dopamine neurons, more accurately reproducing the pattern of neuropathological and neurochemical alterations observed in idiopathic PD.

Recent advances of *in vivo* receptor studies have resulted in the development of new receptor specific ligands [2, 23, 32, 33, 63] combined with advances in

instrumentation for PET [3, 11, 16]. High resolution positron imaging yields accurate data over small regions inside the brain [9] that, combined with modeling of the ligand-receptor interaction, can provide valuable quantitative information about receptor behavior in different areas of the living brain.

Modeling of neuroreceptor kinetics has also been an active research area. Several methods have been proposed for estimating the binding parameters (B_{\max} , maximum available receptor binding sites; K_D , dissociation constant; k_{on} , bimolecular association rate constant; and k_{off} , dissociation rate). The choice of method depends on the particular properties of ligand-receptor interaction. In reversible binding, ligands dissociate from the receptor during the imaging period so that the maximum binding site density can be calculated from the equilibrium distribution [23]. In the case of irreversible binding, equilibrium is not achieved during the imaging period. The dopamine transporter specific ligand (¹¹C-CFT) has irreversible binding.

Two types of kinetic analysis are used to analyze PET data. The graphical method [60, 73] has been applied by our group to estimate the influx of ¹¹C-CFT to dopamine terminals [42], and by several groups in estimating the influx of L-6-¹⁸F-fluorodopa [59, 67]. The other method is based on general non-linear regression techniques [14, 61, 69, 77].

Research has demonstrated a significant correlation between depression of striatal ¹⁸F-L-fluorodopa uptake of PD patients and their degree of locomotor disability. However, while the average putamen ¹⁸F-L-dopa uptake in PD is reduced to 40% of normal, a 60% loss of nigra compacta cells and 80–90% loss of putaminal dopamine levels are found post-mortem in PD [34]. Therefore, striatal ¹⁸F-L-fluorodopa uptake reflects metabolic and functional activity of nigro-striatal fibers, but may not accurately depict levels of endogenous striatal dopamine or anatomical depletion of dopamine terminals. A specific tracer for selective labeling of dopamine fibers would be preferable. Among various candidates for labeling dopaminergic fibers, specific ligands for dopamine re-uptake sites (dopamine transporter) such as ¹¹C-nomifensine, ¹¹C-cocaine or ¹⁸F-GBR 13119 (1-((4-((18F)fluorophenyl) (phenyl)methoxy) ethyl)-4-(3-phenylpropyl) piperazine) have been used in PET studies [27, 50, 57]. In such PET studies, specific binding of the ligands to dopamine transporters were taken as a measure of monoaminergic nerve terminal density. However, using these ligands *in vitro*, binding assay showed only a 40% decrease of binding in the caudate nucleus and putamen of subjects with PD [65], while other measures for

dopaminergic terminals were reduced much more dramatically. Similar results have been obtained in vivo using ^{11}C -S-nomifensine as a PET tracer [58]. Again, the 40% decrease in dopamine re-uptake site density is strikingly different from the 90% decrease of dopamine levels measured post-mortem in parkinsonian putamen.

We have studied the imaging characteristics of carbon-11 labeled CFT in normal and MPTP-treated primates [10], and it has proved to be a very selective ligand [68] to monitor dopamine terminal degeneration having higher specificity than nomifensine or GBR analogues for the dopamine uptake complex [49]. Several observations suggest that CFT is a useful and specific marker for dopamine nerve terminal density: ^{11}C -CFT in vivo binding, as well as ^3H -CFT in vitro binding [49] in the non-human primate caudate nucleus, is highly specific for the dopamine transporter. ^3H -CFT binding was decreased in PD up to 95% depending on striatal region [49], and ^3H -CFT depletion in PD paralleled the dopamine depletion, with a more severe decrease in specific binding in the putamen than in the caudate nucleus [49].

Our group was the first to demonstrate that ^{11}C -CFT binding correlated with behavioral symptoms in a primate model of Parkinson's disease [42]. This has been verified in a larger series of primates [81], and also in early Parkinson's disease in humans [32]. After the earlier studies, several novel tropane derivatives have been introduced for imaging of dopamine transporters, mainly labeled with iodine-123 (altropane [64], beta-CIT [22], FP-CIT [7], PE21 [38] or technetium-99m (trodat) [53].

Figure 1 shows that the radiolabeled cocaine analog ligands e.g., ^{11}C -CFT provide better sensitivity and selectivity for imaging of the striatal dopamine system than radiolabeled L-dopa. Figure 1 also demonstrates the effect of the increased active radiolabeled metabolites during imaging with ^{18}F -L-6-fluorodopa in blood rich areas in the head. ^{11}C -CFT used in PET imaging of MPTP treated monkeys demonstrate progressive DA terminal loss in caudate-putamen before and after appearance of PD signs. In addition, the observed MPTP-induced degeneration is more progressive in putamen than in caudate (figure 2). Our new MRS studies illustrate lactate/lipid elevation in the striatum in both parkinsonian monkeys (post-MPTP) and in a typical case of a Parkinson's disease patient (68 year old male, Hoehn-Yahr scale II). This is consistent with previous studies [8], showing parallel increases in striatal lactate/lipid and continuous DA fiber (^{11}C -CFT) degeneration. In addition, the small decrease in NAA (12%) observed in the monkeys may also be reflective of the

loss of dopamine terminals and striatal cell dendritic density.

Notably in the MPTP monkeys, there was a large increase in the Cho/Cr ratio which was almost identical to that of PD patients (Cho/Cr = 1.2). This is possibly an important physiological observation, since choline may reflect gliosis or macrophage activity. The various theories for neurodegeneration in PD includes one of loss of target-derived trophic support [17, 75, 76]. Glial cells typically provide both growth-factors and homeostatic support [75, 76, 82]. This finding deserves further investigation to determine if sub glial changes are a consequence or a primary cause of dopaminergic axonal degeneration in the caudate-putamen of PD.

Our data provides a basis for a mathematical model of degeneration of the DA system in PD. It is known that 60–70% degeneration in a dopaminergic system precedes the symptoms of PD. In our primate PD model, the remaining entities (dopamine re-uptake sites) were (0.3–0.4) of the original value when the PD signs appeared. Interestingly, this biological degenerative phenomena has similar progression to that formulated in cell survival theory in radiobiology concerning the effect of radiation in killing cells [41]. According to the formula, the number of survived cells (N_D) after radiation dose (D) is $N_D = N_0 \exp(-D/D_0)$, where N_0 is the number of cells before radiation and D_0 is the mean lethal dose of radiation. When the radiation dose (D) equals to the mean lethal dose (D_0), the function will get a form of $N_D/N_0 = e^{-1} = 0.37$ and the number of survived cells is $0.37 N_0$. Similarly, using the rate of degeneration (0.072 ± 0.016 , figure 3), the calculated time to get PD signs is 13.9 ± 2.5 months in this MPTP-PD model, which is the same as was observed in experimental studies (figure 3). With this theory and imaging studies of the dopaminergic system, a realistic estimate can be obtained of degeneration rate and the time when the patient will get PD symptoms.

CONCLUSION

^{11}C -CFT is a useful ligand for detection of PD-like progressive degeneration. Based on the decrease of ^{11}C -CFT binding, a rate of degeneration can be calculated and the time of onset of PD symptoms can be determined.

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