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PARAQUAT IS EXCLUDED BY THE BLOOD BRAIN BARRIER IN RHESUS MACAQUE: AN IN VIVO PET STUDY

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Abstract

Environmental factors have long been thought to have a role in the etiology of idiopathic Parkinson's Disease (PD). Since the discovery of the selective neurotoxicity of MPTP to dopamine cells, suspicion has focused on paraquat, a common herbicide with chemical structure similar to 1-methyl-4-phenylpyridinium (MPP⁺), the MPTP metabolite responsible for its neurotoxicity. Although in vitro evidence for paraquat neurotoxicity to dopamine cells is well established, its in vivo effects have been ambiguous because paraquat is di-cationic in plasma, which raises questions about its ability to cross the blood brain barrier. This study assessed the brain uptake of [¹¹C]-paraquat in adult male rhesus macaques using quantitative PET imaging. Results showed minimal uptake of [¹¹C]-paraquat in the macaque brain. The highest concentrations of paraquat was seen in the pineal gland and the lateral ventricles. Global brain concentrations including those in known dopamine areas were consistent with the blood volume in those structures. This acute exposure study found that paraquat is excluded from the brain by the blood brain barrier and thus does not readily support the causative role of paraquat exposure in idiopathic Parkinson's Disease.

Keywords

Paraquat; Parkinson's disease; blood-brain barrier; rhesus macaque; PET imaging

INTRODUCTION

Paraquat (1,1'-dimethyl-4,4'-bipyridium dichloride) (Figure 1) is a common herbicide with close chemical structural resemblance to MPP⁺ (1-methyl-4-phenylpyridinium), the toxic metabolite of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a well-established selective toxin for dopamine cells (Javitch et al. 1985). Numerous studies have reported on the possible causative role of paraquat in Parkinson's disease (PD) based on this chemical homology. Since paraquat dichloride is a di-cation in blood, doubts regarding its neurotoxicity were raised early on (Koller 1986) and again recently (Miller 2007) because of the blood brain barrier (BBB). While it is clear from in vitro studies that paraquat is toxic to dopamine cells (McCormack et al. 2005; Fei et al. 2008), achieving in vivo brain concentrations required for

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toxicity has been questioned (Miller 2007). The confusion regarding the role of paraquat in PD has been exacerbated by ambiguity of data on the ability of paraquat to cross the blood brain barrier. Many rodent studies have reported the ability of systemic paraquat administration to induce parkinsonism (Corasaniti et al. 1992a; Shimizu et al. 2001; Li et al. 2005; Prasad et al. 2007;). But others (Naylor et al. 1995; Widdowson et al. 1996) find the contrary, including a recent study on chronic inhalation of paraquat in rodents which was found not to induce dopaminergic neurotoxicity (Rojo et al. 2007). To clarify the issue of blood brain barrier penetration of systemic paraquat, this study was undertaken to assess the uptake of [^{11}C] paraquat in the non-human primate brain in vivo using quantitative PET imaging.

RESULTS

Figure 2 displays both axial and sagittal views of one monkey brain at early, mid, and late time points after [^{11}C]paraquat injection, providing visualization of the pharmacokinetics of the radiotracer. The early image set is the first frame of the study collected over the first 60 sec after injection, reflects the blood delivery of paraquat to all cerebral and extracerebral regions and [^{11}C] intensity is related to perfusion. The second image set is an average of frames corresponding to 3–8 min post-injection, shows exclusion of paraquat from brain tissue with significant uptake remaining in extracerebral cranial muscle (axial view) and nasopharynx (sagittal view). The last set of images corresponding to 50–80 min post-injection, show that paraquat remains excluded from brain tissue and the reduced levels in muscle and nasopharynx indicate tracer clearance.

Figure 3 presents axial (A) and sagittal (B) views of the fused PET/MR images after averaging PET frames over the final 50 minutes of the study to better delineate brain tissues for placement of ROIs. The fused PET/MR images demonstrate low cerebral, relative to extracerebral, [^{11}C] paraquat signal. The axial (A) view shows some paraquat localization in the posterior horns of the lateral ventricles (LV), denoted by the arrows, while the sagittal view (B) indicates paraquat localization in the pineal gland (PG).

Time courses of the standardized uptake values (SUV) averaged over the four subjects in four cerebral regions are presented in Figure 4. In these plots, the SUV time courses for the caudate nucleus (A), putamen (B), lateral ventricles (C) and pineal gland (D) are plotted along with the blood-volume-scaled bi-exponential fitted plasma curve. The observed high correlation between the time-activity curves (TAC) for the caudate and putamen and the scaled plasma curve suggests that the [^{11}C]paraquat tissue concentration is associated primarily with blood vessels in those regions. On the other hand, the lateral ventricles and pineal gland radioactivity curves decrease in concentration more slowly than the blood curve, indicating that paraquat is clearing more slowly from these structures than from blood. At the end of the scan, the pineal gland, the only tissue to exhibit identifiable uptake, had residual paraquat concentrations in the range of 0.002 – 0.003% injected dose/cc in the four animals. For comparison, studies using the radiotracer [^{18}F]Fallypride, which avidly bind dopamine D2 receptors, has 0.032 – 0.070% injected dose/cc bound in the striatal regions (Bartlett *et al.*, unpublished) at the same post-injection time. The TAC for the substantia nigra falls at the same rate as the plasma TAC but with an apparent excess at later times (data not shown). This excess is likely due to spillover from nearby extracerebral paraquat accumulation since the substantia nigra is adjacent to extracerebral paraquat pools with radioactivities on the order of 12 – 20 KBq/cc at a distance less than the 6 mm resolution of the PET scanner. Partial volume effects decrease the observed concentration in areas of accumulation and increase the observed concentration in neighboring areas, the substantia nigra in this case, confounding the generated SUV time course in this region.

DISCUSSION

The finding that MPTP caused parkinsonism (Langston et al. 1983) and the subsequent identification of its metabolite MPP⁺ as the selective toxin for dopamine neurons (Javitch et al. 1985) buttressed the idea that environmental chemicals have a role in idiopathic PD. Paraquat was first suggested as an environmental agent with potential causative role in PD because of the similarity of its chemical structure to MPTP and MPP⁺ (Barbeau et al. 1985) (Figure 1). Since then, many studies have either supported or found no support for this hypothesis. The key question raising doubt about the role of paraquat in PD is its ability to cross the blood brain barrier (Koller 1986) and reach neurotoxic levels (Miller 2007). Many rodent studies done to explore this issue have not provided a definitive answer to this question. While there are numerous studies on BBB penetration of paraquat in rodents that report damage to dopamine cells leading to parkinsonism (Lindquist et al. 1988; Corasaniti et al. 1991; Corasaniti et al. 1992a; Corasaniti et al. 1992b; Corasaniti and Nistico 1993; Shimizu et al. 2001; Li et al. 2005; Prasad et al. 2007), other studies report minimal rodent brain paraquat uptake (Naylor et al. 1995, Widdowson et al. 1996). Widdowson et al. (1996) report that multiple oral paraquat treatments do not result in changes in behavior, nigrostriatal neurochemistry or neuropathology. On the contrary, Kuter et al. (2007) recently found that sub-chronic paraquat administration in rats decreased the number of tyrosine hydroxylase-immunoreactive (TH-ir) neurons in the substantia nigra, triggered processes characteristic of early stages of dopaminergic neuron degeneration, and activated compensatory mechanisms involving monoaminergic and GABAergic transmissions, effects only possible if brain uptake reaches neurotoxic levels. Chronic paraquat inhalation, a possible route of environmental paraquat exposure, was reported to have no role in the development of PD in mice and rats (Rojo et al. 2007). Taken all together, these conflicting results have not provided a clear answer to the question of whether paraquat is transported across the blood brain barrier.

There are a few primate brain uptake studies of paraquat in the literature and none specifically addressed the issue of BBB transport (e.g., Murray and Gibson 1974). More informative on the mechanisms of paraquat toxicity are hundreds of reported cases of human poisoning due to accidental or deliberate ingestion in suicides (Lee et al. 2002, Dinis-Oliveira et al. 2008). Acute paraquat poisoning leads to death mainly as a result of extensive pulmonary fibrosis (Paraquat lung), extensively reviewed recently by Dinis-Oliveira et al. (2008). Renal, hepatic and pancreatic failures after paraquat intoxication have also been reported to underlie the lethality of paraquat poisoning in humans (Lee et al. 2002). Of relevance to this report are post-mortem examinations of brains of persons who died of paraquat poisoning that found regional brain tissue damage (Grant et al. 1980; Hughes 1988).

Visual examination of the PET images in Figures 2 and 3 suggest that there is minimal paraquat uptake and retention in the whole primate brain. The SUV curves shown in Figure 4 provide quantitative evidence of paraquat's regional brain sequestration. Paraquat is weakly sequestered by specific brain structures, namely, the pineal gland (C) and the lateral ventricles (D). But the tissue time courses indicate no selective accumulation of paraquat in the dopamine terminals located at the caudate nucleus (A) and putamen (B) but rather close association with plasma radioactivity. This is consistent with rodent studies that reported the high correlation of cerebral distribution of [¹⁴C]paraquat 24 h after systemic administration with cerebral blood volume (Naylor et al. 1995). Other rodent studies, however, report paraquat accumulation in striatum and the substantia nigra (Shimizu et al. 2001; McCormack and Di Monte 2003). The reason for these discrepancies in rodents is unclear.

The images and tissue time courses (Figures 2–4) clearly show that 90 minutes after systemic injection, the remaining cerebral paraquat was largely confined to the pineal gland and the lateral ventricles, both of which lack a BBB. Again this is consistent with the rodent studies

of (Naylor et al. 1995) that report “most of the [^{14}C]paraquat was associated with five structures, two of which, the pineal gland and linings of the cerebral ventricles lie outside the blood/brain barrier whilst the remaining three brain areas, the anterior portion of the olfactory bulb, hypothalamus and area postrema do not have a blood/brain barrier.” Furthermore, results of this non-human primate study also agree with results of post-mortem examination of brains of eight people who died of paraquat poisoning. Grant et al.(1980) consistently found significant generalized brain edema and hemorrhages in CSF-associated (subependymal and subarachnoid) blood vessels. Similar findings were reported by Hughes (1988) who report brain damage around the lateral and third ventricles in the brain of a 20-yr old suicide victim who died after ingesting 50–100 ml of a 20% solution of paraquat.

In conclusion, the finding of minimal cerebral uptake of [^{11}C]paraquat in rhesus macaque brains observed in this study with PET imaging does not readily support the etiologic role of paraquat exposure in idiopathic Parkinson’s disease. Such minimal uptake suggests that extraordinary exposure, e.g., high dose and extensive chronicity, would likely be needed to cause selective striatal and/or nigral damage leading to significant pathology in nigrostriatal dopamine neurons and eventual Parkinson’s disease. Notwithstanding these findings, the possibility that cumulative paraquat exposure may lead to neurodegeneration and PD is not discounted by these results especially since chronic paraquat exposure may gradually damage the BBB and allow toxic paraquat levels to accumulate in dopamine cells or possibly, as Purisalet al.(2007) suggested, initiate priming events predisposing dopamine neurons to damage by subsequent insults. On the other hand, the unfettered access of paraquat to peripheral organs notably the lungs, heart, liver, kidneys and pancreas would suggest that the failure of these organs (Beligaswatte *et al.* 2008; Lee *et al.* 2002) rather than dopamine neuronal damage would be of more concern in any chronic exposure scenario. Other possible effect-modifying scenarios include the synergistic effects of co-exposure with other agents as maneb (Barlow et al. 2005), iron (Peng et al.2007) or other agents, or a compromised BBB due to infection, trauma, or in utero exposure, may allow neurotoxic levels of paraquat to be reached. Finally, unknown epigenetic effects related to paraquat exposure may also be involved in the development of idiopathic PD.

EXPERIMENTAL PROCEDURE

Chemicals and Materials

Paraquat dichloride and 4,4'-bipyridine (dipyridyl) were purchased from Sigma-Aldrich Chemicals Inc. (St. Louis, MO). The precursor to prepare [^{11}C -methyl]-paraquat, des-methyl-paraquat (1-methyl-4,4'-bipyridium dichloride) was prepared by mono-methylating 4,4'-bipyridine (dipyridyl) by treatment with methyl iodide in methylene chloride. The pale yellow quaternary ammonium iodide salt of 1-methyl-4,4'-bipyridine was then converted using aqueous silver triflate to the corresponding quaternary ammonium triflate salt (Figure 1) as a yellowish white crystalline solid.

Radioligand Preparation

[^{11}C -methyl]-Paraquat was prepared using a published method (Jewett 2002) which involved the reaction of [^{11}C]methyl triflate prepared from [^{11}C]methyl iodide (Jewett 1992) with the 1-methyl-[4,4']bipyridine mono-triflate salt described above. Reverse-phase high performance liquid chromatographic (HPLC) separation of the product was carried out on a 10 μ Econosphere silica semipreparative (10 $\times$ 250mm) column (Alltech Associates, Deerfield, IL). Mobile phase was 65:35 mixture of acetonitrile and 0.8% NaCl aq. solution previously adjusted to a pH of 2.0 with HCl. The HPLC fraction containing the [^{11}C]paraquat peak was collected, the mobile phase was evaporated and [^{11}C]paraquat product was then reconstituted in sterile

saline followed by sterilization by filtration with 0.22 micron Millipore filter prior to injection to the rhesus macaques. Specific activity range of [^{11}C]paraquat was 210 – 1500 Ci/mmol.

PET Scanning

Four healthy adult male rhesus monkeys (*Macaca Mulatta*) (10–13 kg) were used for the PET studies. The animal care and use procedures for all experiments were approved by the Institutional Animal Care and Use Committee of the University of Wisconsin Madison in compliance with NIH regulations on the use of non-human primates in research. The animals were anesthetized with ketamine (15 mg/kg intramuscular) to permit transport and subsequently maintained on 1–2% isoflurane for the duration of the PET study. The anesthetized animal was positioned prone in the scanner bed with its head comfortably immobilized in a stereotactic head holder orienting the brain such that the PET slices paralleled the orbitomeatal (OM) line. [^{11}C]Paraquat (dose range: 3.0 – 6.1 mCi; 0.1 – 0.4 $\mu\text{g/kg}$) was administered through an intravenous catheter placed in the animal's saphenous vein.

PET images were acquired on a Siemens ECAT EXACT 921 scanner (Siemens/CTI, Knoxville, USA), with a 16.2 cm axial field-of-view (FOV) and 5 mm axial and 6 mm transaxial resolution. Emission data was collected in 3D mode to maximize sensitivity. A five-minute transmission scan was acquired prior to radiotracer administration for post-acquisition correction of the emission data using segmented attenuation correction. A dynamic scanning sequence consisted of four 1 minute-frames, three 2 minute-frames, two 5 minute-frames, and seven 10 minute-frames for a total acquisition time of 90 minutes. Scanning was initiated concurrently with bolus infusion of the radiotracer (5 ml infused over 30 seconds).

The raw PET data was corrected for deadtime, randoms, scatter, attenuation, and normalization. The images were reconstructed into a 128 $\times$ 128 (transverse) $\times$ 47 (axial) image matrix using a 6 mm Gaussian filter and filtered back-projection.

Approximately 1 ml venous blood samples were collected throughout the dynamic imaging sequence. Blood sampling was initiated with injection of radiotracer with rapid samples drawn initially (one sample every 15 seconds for the first 120 seconds) and less frequently toward the end of the study (one sample every 15 minutes). Blood was added to centrifuge tubes containing 10 USP units of heparin. After gentle mixing, samples were centrifuged for five minutes at 5000 rpm and 4 $^{\circ}\text{C}$ (Heraeus Sepatech, Biofuge 17RS, Germany). 0.4 ml plasma were aliquoted into pre-weighed vials, weighed, and counted to assess the radioactivity concentration using a well counter with 3" $\times$ 3" NaI(Tl) detector. Metabolite analysis was not performed based on literature report that paraquat is excreted largely unchanged via the kidneys (Daniel and Gage 1966).

Each of the monkeys had previously undergone magnetic resonance imaging (MRI) on an Advantix 1.5 T instrument (General Electric Medical Systems, Waukesha, WI). MR imaging included a spoiled gradient-echo (SPGR) sequence, and a 3D acquisition reconstructed into contiguous 1.3 mm coronal slices. This provided good differentiation between gray and white matter that allowed delineation of cerebral structures.

PET Data Analysis

MRI images were anatomically co-registered with each of the respective PET scans for quantitative assessment. Co-registration was performed manually using the software package Amira 4.1 (Mercury Computer Systems, Chelmsford, MA).

Regions of interest (ROIs) including: caudate nucleus, putamen, substantia nigra, and lateral ventricles were identified based on the anatomical information provided by the MR image. Time-activity curves (TACs) defining regional tissue radioactivity concentration kinetics were

generated from the dynamic PET data for each contoured ROI. To allow comparison across animals, the TACs were normalized to standardized uptake values (SUVs, calculated as [(ROI activity in MBq/cc) $\times$ (body weight in kg)]/[(total injected dose in MBq)]).

Plasma Analysis

Radioactivity in each plasma sample was decay-corrected then normalized for animal weight and injected dose to allow comparison across monkeys, and plotted against time to generate plasma time-activity curves (TACs). The mean plasma TAC (n=4) was fitted to a bi-exponential function of time ($R^2 = 0.849$) scaled to fractional mean cerebral blood volume (CBV) of 5 ml/100g in grey matter as reported in the literature (Eichling *et al.* 1975; Phelps *et al.* 1973).

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Figure 1.
Chemical structures of MPTP and its metabolite, MPP⁺, and paraquat dichloride and its des-methyl precursor, 1-methyl-bipyridine triflate.

Figure 2.

PET images of $[^{11}\text{C}]$ Paraquat in adult male rhesus macaque brain. The images are displayed in two orientations, axial and sagittal, at three time points – early and the averages of the time frames corresponding to mid (3–8 minutes) and late (50–80 minutes) post-injection times. Radioactivity is displayed using the hot metal scale shown.

Figure 3.

Fused PET/MR images of [^{11}C]Paraquat in adult male rhesus macaque brain displayed in axial (A) and sagittal (B) orientations. [^{11}C]Paraquat PET images were averaged over the last 50 minutes of the study. The arrows indicate the posterior lobes of the lateral ventricles (2A) and the pineal gland (2B). Note that most of the radioactivity is extra-cerebral (muscle, nasopharynx, etc.).

Figure 4.

Average SUV curves (n=4) of brain structures plotted with the fitted plasma SUV curve (scaled to 5% CBV). The brain structures are caudate nucleus (A), putamen (B), lateral ventricles (C) and pineal gland (D). The plots indicate that the only structures to clear paraquat slower than the blood are the lateral ventricles (C) and the pineal gland (D).