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Examining Endogenous Dopamine in Treated Schizophrenia using [¹¹C]-(+)-PHNO Positron Emission Tomography: A Pilot study

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Abstract

Background—Using positron emission tomography (PET) it is possible to estimate endogenous dopamine (DA) occupying D_{2/3} receptors (D_{2/3}R) in the living human brain. Persons with schizophrenia (SZ) (previously medicated and naïve) have increased endogenous DA occupying D_{2/3}R in the caudate. It is unknown whether currently medicated patients demonstrate increased DA levels at D_{2/3}R. Moreover, DA levels have not been estimated in SZ using agonist radiotracers, which may offer a more sensitive quantification over antagonists.

Methods—Using the agonist radiotracer [¹¹C]-(+)-PHNO, DA levels were estimated at D_{2/3}R (BP_{ND}) in three patients with SZ (Male, Mage=30±16). Patients were currently being treated long-term with Olanzapine (147±88 nmol/L). Results were compared to ten healthy controls (HC's).

Results—Medicated persons with SZ had greater BP_{ND} in the left caudate (U=2, Z=-2.20, p=.03) and right putamen (U=2, Z=-2.20, p=.03). No differences were observed in the ventral striatum or globus pallidus.

Conclusions—It is possible to estimate endogenous DA at D_{2/3}R in SZ patients currently taking antipsychotics. Despite medication, patients continue to have increased endogenous DA at D_{2/3}R. This lends more biological support to the clinical observation that relapses in symptoms can occur

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in the face of complete antipsychotic discontinuation. Future studies with larger samples are warranted.

Keywords

PET; Dopamine; D₂/3R; Schizophrenia

Introduction

Schizophrenia is a severe and chronic mental illness which affects 1% of the population, ranking as one of the leading causes of disability worldwide [1, 2]. While the cause of schizophrenia is currently unknown, the “dopamine (DA) hypothesis of schizophrenia” has been the most enduring idea in psychiatry for the last fifty-years [3]. Thus, long before advanced brain imaging, it was hypothesized that abnormally high levels of the neurochemical DA would be present in the brains of persons with schizophrenia [4].

Positron emission tomography (PET) is an *in vivo* molecular imaging technique which can allow measurement of protein molecules such as DA receptors. Using PET and radiolabelled DA D₂/3 receptor (D₂/3R) antagonists, such as [¹¹C]-raclopride, [¹⁸F]-fallypride, and [¹¹C]-FLB 457, it has been possible to quantify the availability of D₂/3R in the brains of healthy persons and persons with neuropsychiatric disease *in vivo* [5–7]. Endogenous DA competes with these radiotracers for binding to D₂/3R at baseline [8]. Thus, increasing DA levels in the brain can decrease radiotracer binding and *vice-versa*. Thus changes in radiotracer binding given challenges which alter DA levels can reveal estimates of DA release and endogenous tone [9].

Using PET and a dopamine depletion challenge it is possible to estimate endogenous DA occupying DA D₂/3 receptors in the living human brain [10, 11]. Using this method, it has been demonstrated that individuals with schizophrenia (previously medicated and antipsychotic naïve) have increased endogenous DA occupying D₂/3R (D₂/3R) in the dorsal striatum – in particular the caudate [12, 13]. However, it is unknown whether patients *currently* taking antipsychotics still demonstrate increased endogenous DA levels at the D₂/3R. Moreover, endogenous dopamine levels in patients with schizophrenia have only been estimated using the antagonist radiotracer [¹¹C]-raclopride, which has similar affinity for D₂R and D₃R.

Our group has developed [¹¹C]-(+)-PHNO [14], the first agonist radiotracer for D₂/3R which has preferential affinity for D₃ receptors [15–18]. As an agonist, this radiotracer is more sensitive to changes in endogenous DA [19, 20] and may provide a more sensitive and physiologically meaningful estimate of endogenous DA occupying D₂/3R in the brains of healthy persons and persons with schizophrenia [21]. Moreover, it can provide estimates of endogenous DA in D₃R rich brain regions not previously explored specifically in persons with schizophrenia, such as the globus pallidus [21].

The current investigation sought to address whether patients *currently* taking antipsychotics have increased endogenous DA in the striatum. This was accomplished using the alpha-

methyl-para-tyrosine (AMPT) DA depletion challenge with PET and [^{11}C]-(+)-PHNO to quantify endogenous DA levels

Methods

The radiosynthesis of [^{11}C]-(+)-PHNO, acquisition/analysis of PET images, and the DA depletion paradigm were identical to those described in detail elsewhere [14, 21]. Patients with schizophrenia received two PET scans: one during a baseline state and another during acute DA depletion. Baseline scans occurred before depletion scans and were at least two days apart. Depletion was induced by oral administration of 64 mg of AMPT (metyrosine) per kilogram of body weight over 25 hours.

The estimate of endogenous DA at $\text{D}_{2/3}\text{R}$ is based on the occupancy model [8, 10, 11]. This model assumes: i) baseline radiotracer binding (BP_{ND}) to $\text{D}_{2/3}\text{R}$ is confounded by endogenous DA - higher DA concentrations result in lower baseline $\text{D}_{2/3}\text{R}$ BP_{ND} , and, ii) the fractional increase in $\text{D}_{2/3}\text{R}$ BP_{ND} after DA depletion [i.e., $100 \times (\text{Depletion BP}_{\text{ND}} - \text{Baseline BP}_{\text{ND}}) / \text{Baseline BP}_{\text{ND}} = \text{BP}_{\text{ND}}$] is linearly proportional to the baseline DA concentration at $\text{D}_{2/3}\text{R}$. Thus, the BP_{ND} , given appropriate assumptions, is considered a semiquantitative index of endogenous DA levels at $\text{D}_{2/3}\text{R}$ [11].

We also held the following assumptions. If the amount and timing of antipsychotic dosing remains constant between the baseline and DA depleted PET scans, then any increase in [^{11}C]-(+)-PHNO BP_{ND} after depletion should reflect reduced competition by DA. Note that it is assumed that endogenous DA has a higher affinity for $\text{D}_{2/3}\text{R}$ than antipsychotics *in vivo*, and will compete more strongly for newly available binding sites given depletion over antipsychotics.

Results

Three patients with schizophrenia (male, mean age=30±16) being treated long-term with olanzapine underwent two [^{11}C]-(+)-PHNO PET scans: one at baseline and one after acute DA depletion. Data from these patients were compared with previously published data from 10 healthy controls (HC) (4 female, mean age: 29.1±8.39) [21]. For one patient with schizophrenia, we were unable to collect plasma samples of AMPT, homovanillic acid (HVA), 3-Methoxy-4-hydroxyphenylglycol (MHPG), prolactin, and olanzapine (See Table 1). The [^{11}C]-(+)-PHNO BP_{ND} before and after DA depletion in HC and patients with schizophrenia are presented in Figure 1. The BP_{ND} between patients and HC were examined using Mann-Whitney U Tests ($p < 0.05$, two-tailed).

Compared to HC's, medicated persons with schizophrenia had greater BP_{ND} in the left caudate ($U=2$, $Z=-2.20$, $p=.03$), but not in the right ($U=8$, $Z=-1.18$, $p=.29$). They also showed greater BP_{ND} in the right putamen ($U=2$, $Z=-2.20$, $p=.03$), but not the left ($U=10$, $Z=-0.85$, $p=.47$). There was a trend for an increase in BP_{ND} for patients in the left ventral striatum ($U=4$, $Z=-1.86$, $p=.08$). No statistically significant differences were observed in the substantia nigra ($U=10$, $Z=-1.69$, $p=.11$), right ventral striatum ($U=10$, $Z=-0.51$, $p=.69$), left globus pallidus ($U=7$, $Z=-1.35$, $p=.22$), or right globus pallidus ($U=11$, $Z=-0.68$, $p=.57$). (See Figure 2).

Discussion

This preliminary investigation sought to examine whether it is possible to estimate endogenous DA levels in the brains of persons with schizophrenia who are currently taking antipsychotics using PET and an AMPT-challenge. Our data suggest that this is possible, given the assumption of consistent antipsychotic dosing for the baseline and depletion PET scans. It appears that even during chronic treatment with an antipsychotic, patients with schizophrenia demonstrate increased baseline endogenous DA levels in the dorsal striatum at D_{2/3}R. Thus, antipsychotics may not alter endogenous DA levels *per se*, suggesting that they do not alter disease pathology. This would be in keeping with evidence from clinical practice, where symptomatic relapse can be seen in the face of complete antipsychotic discontinuation. Future PET studies should attempt to estimate endogenous DA levels in medication naïve and chronically treated patients with schizophrenia using [¹¹C]-(+)-PHNO and larger sample sizes.

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Highlights

- Dopamine levels were estimated in the brains of medicated schizophrenia patients
- Patients with schizophrenia had more dopamine in the left caudate and right putamen
- Despite being medicated dopamine levels are still high in patients with schizophrenia

Figure 1.

Figure 2.

Table 1

Plasma levels of participants. Ten healthy controls and two patients with schizophrenia.

Plasma Levels	Group	Baseline	AMPT 5h	AMPT 27h	% 27h
Homovanillic Acid (HVA) nmol/L	Healthy Controls	81.8 (42.8)	37.0 (15.0)	32.4 (27.2)	-60%
	Medicated Patients	84.2 (35.5)	43.4 (31.9)	17.6 (0.8)	-72%
3-Methoxy-4-hydroxyphenylglycol (MHPG) nmol/L	Healthy Controls	188.3 (99.2)	160.5 (89.2)	109.5 (60.3)	-42%
	Medicated Patients	161.2 (44.9)	141.3 (31.4)	104.9 (22.3)	-38%
Prolactin ng/mL	Healthy Controls	13.0 (9.6)	36.8 (21.4)	25.5 (10.4)	135%
	Medicated Patients	20.7 (6.8)	35.7 (8.1)	32.0 (11.1)	56.3%
Alpha-methyl-prara-tyrosine (AMPT) umol/L	Healthy Controls		63.1 (38.2)	123.0 (53.0)	
	Medicated Patients		75.7 (23.9)	57.2 (12.7)	
Olanzapine (nmol/L)	Medicated Patients	147 (88)	136 (80)	144 (84)	-2%