Molecular Psychiatry
https://doi.org/10.1038/s41380-020-00879-0

ARTICLE

Dopamine dysregulation in psychotic relapse after antipsychotic discontinuation: an [^{18}F]DOPA and [^{11}C]raclopride PET study in first-episode psychosis

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Received: 22 February 2020 / Revised: 24 August 2020 / Accepted: 3 September 2020
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Abstract

Although antipsychotic drugs are effective for relieving the psychotic symptoms of first-episode psychosis (FEP), psychotic relapse is common during the course of the illness. While some FEPs remain remitted even without medication, antipsychotic discontinuation is regarded as the most common risk factor for the relapse. Considering the actions of antipsychotic drugs on presynaptic and postsynaptic dopamine dysregulation, this study evaluated possible mechanisms underlying relapse after antipsychotic discontinuation. Twenty five FEPs who were clinically stable and 14 matched healthy controls were enrolled. Striatal dopamine activity was assessed as K_i^{cer} value using [^{18}F]DOPA PET before and 6 weeks after antipsychotic discontinuation. The D2/3 receptor availability was measured as BP_{ND} using [^{11}C]raclopride PET after antipsychotic discontinuation. Healthy controls also underwent PET scans according to the corresponding schedule of the patients. Patients were monitored for psychotic relapse during 12 weeks after antipsychotic discontinuation. 40% of the patients showed psychotic relapse after antipsychotic discontinuation. The change in K_i^{cer} value over time significantly differed between relapsed, non-relapsed patients and healthy controls (Week*Group: $F = 4.827$, df = 2,253.193, $p = 0.009$). In relapsed patients, a significant correlation was found between baseline striatal K_i^{cer} values and time to relapse after antipsychotic discontinuation ($R^2 = 0.518$, $p = 0.018$). BP_{ND} were not significantly different between relapsed, non-relapsed patients and healthy controls ($F = 1.402$, df = 2,32.000, $p = 0.261$). These results suggest that dysfunctional dopamine autoregulation might precipitate psychotic relapse after antipsychotic discontinuation in FEP. This finding could be used for developing a strategy for the prevention of psychotic relapse related to antipsychotic discontinuation.

Introduction

First-episode psychosis (FEP) is characterized by heterogeneity in clinical presentation and outcome [1, 2]. Based

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Published online: 14 September 2020

on the current diagnostic criteria, it includes various mental illnesses such as brief psychotic disorder, schizophrenia, and affective spectrum psychoses; these demonstrate different clinical trajectories and prognoses [3]. Nonetheless, FEP manifests psychotic symptoms by definition and antipsychotic drugs are used as treatment.

Psychotic symptoms in FEP appear to be related to alteration of the dopamine system. Indeed, a meta-analysis identified elevated presynaptic dopamine synthesis and release capacity in schizophrenia [4]; moreover, the severity of psychotic symptoms measured by using the Positive and Negative Syndrome Scale (PANSS) was associated with the extent of the elevation of dopamine synthesis capacity [5]. Furthermore, elevated presynaptic dopamine capacity was also observed in patients who had bipolar disorder with psychotic symptoms, while bipolar disorder without psychotic symptoms did not show elevated dopamine synthesis capacity [6]. These results suggest a transdiagnostic role of dopamine dysregulation in the pathophysiology of psychotic symptoms [6].

Considering the presynaptic dopamine abnormalities underlying psychotic symptoms, it is plausible that the pharmacological actions of antipsychotic drugs may be exerted by blocking the postsynaptic dopamine receptors and consequently reducing the overflow of dopaminergic neurotransmission from the presynaptic area. The mechanism of antipsychotic action is supported by the findings from schizophrenia studies; specifically, the level of presynaptic dopamine synthesis capacity was associated with responsiveness to first-line antipsychotic drugs, which primarily block dopamine D2 receptors [7, 8].

Antipsychotic drugs are generally effective for ameliorating psychotic symptoms, and the majority of patients with FEP initially achieve remission [9, 10]. However, psychotic relapse is often encountered during the course of the illness, and antipsychotic discontinuation is reported to be the most common risk factor [11, 12]. The rate of psychotic relapse was reported to be as high as more than 45% at 1 year after antipsychotic discontinuation [13, 14], although the rate differed depending on the definition of the relapse and the follow-up period. Therefore, many clinicians tend to continue administration of antipsychotic treatment to prevent relapse. However, long-term follow-up studies showed that antipsychotic dose reduction or discontinuation could be more beneficial than medication maintenance in terms of cognition and/or social function [11, 15]. Furthermore, some patients with FEP remained in long-term remission, despite antipsychotic discontinuation [2, 16, 17]. The high rate of psychotic relapse after antipsychotic discontinuation in FEP, as well as the benefit from successful antipsychotic discontinuation in some FEP, indicate an urgent need to identify predictors of the successful discontinuation or psychotic relapse.

Some studies have focused on clinical features to identify predictors of psychotic relapse after antipsychotic discontinuation in patients with FEP; these predictors included a diagnosis of cannabis use disorder, longer duration of antipsychotic treatment, male sex, and number of previous psychiatric hospital admissions [13, 14]. These predictors have limited success in that they do not reflect the biological mechanism of psychotic relapse after antipsychotic discontinuation.

As mentioned above, psychotic symptoms are reportedly related to the elevation of presynaptic dopamine activity [18–20]. Persistent elevation of presynaptic dopamine activity, despite antipsychotic treatment, might precipitate psychotic relapse after antipsychotic discontinuation in FEP (Hypothesis 1). Meanwhile, some studies have proposed a normalizing or stabilizing effect of antipsychotic drugs on dopaminergic neurotransmission [21–23], although this effect remains controversial [19]. When the effects of an antipsychotic drug, which might have presumably normalized the dopaminergic dysregulation in clinically stable FEP, fade away after the discontinuation, a progressive increase of dopamine synthesis would develop, which may be related to psychotic relapse after antipsychotic discontinuation (as observed in subjects at high risk for psychosis) (Hypothesis 2) [24]. Another possible mechanism for psychotic relapse after antipsychotic discontinuation can be inferred from the effect of antipsychotic drugs on dopamine receptors. Prolonged blockade of dopamine D2 receptors by antipsychotic drugs is presumed to upregulate the receptors, developing so-called dopamine hypersensitivity [25, 26]. The receptor upregulation and related dopamine hypersensitivity could explain psychotic relapse after withdrawal from antipsychotic treatment (Hypothesis 3).

In this study, we aimed to evaluate three possible dopamine dysregulation mechanisms underlying psychotic relapse after antipsychotic discontinuation. For this, we enrolled FEP who responded well to first-line antipsychotic drugs; thus, they were considered to have dopamine dysregulation as the underlying pathophysiology of their psychotic symptoms [7, 8]. To investigate a possible persistent elevation of presynaptic dopamine activity (Hypothesis 1) and/or its change after antipsychotic discontinuation (Hypothesis 2), we employed [^{18}F]DOPA positron emission tomography (PET) before and after the discontinuation. To test the upregulation of D2/3 receptors and its relationship to psychotic relapse (Hypothesis 3), we measured the availability of striatal dopamine D2/3 receptors by using [^{11}C]raclopride PET after antipsychotic discontinuation. FEP enrolled in this study were prospectively followed up to monitor psychotic relapse after antipsychotic discontinuation, and the relationship between dopamine dysregulation and psychotic relapse was investigated.

Subjects and methods

The present study was approved by the Institutional Review Board of Seoul National University Bundang Hospital, Gyeonggi-do, Korea, and conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Participants

Participants (aged 19–45 years) received a full explanation of the study and provided written informed consent to participate. Screening procedures included physical examination, checking vital signs, laboratory tests (hematology, blood chemistry, and urinalysis), and a 12-lead electrocardiogram. Subjects with any medically significant abnormalities were excluded.

Patients were recruited from the FEP clinic in the Seoul National University Bundang Hospital. Patients who met the following inclusion criteria were invited to participate in the study: (1) patients who had experienced their first psychotic episode exhibiting hallucination, delusion and disorganized behaviors with functional impairment within 2 years before enrollment; (2) patients who had continuously received adequate doses of antipsychotic treatment for at least 1 year [27]; (3) patients who had a total score of ≤80 on the PANSS and no items with a score >4 on the positive subscale of the PANSS; (4) patients had to have no history of hospitalization for at least 3 months before the participation in the study; (5) patients with no clinical reasons for antipsychotic discontinuation, including an imminent risk of suicide and/or violence; and (6) patients with no history of lifetime substance abuse or dependence. The diagnoses of the patients were assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version (SCID-I/P) [28].

Healthy controls were recruited via advertisement and were matched to the patients based on age and sex. A psychiatric interview for screening of unidentified conditions was conducted using the Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient edition (SCID-I/NP) [29].

Study design

Figure 1 illustrates the study design. After enrollment, patients received their first [^{18}F]DOPA PET scans (baseline) with no change in their maintenance treatment. After the first [^{18}F]DOPA PET scan, antipsychotic discontinuation was completed within 4 weeks at the rate of 25% reduction in dosage per week. Other concurrently prescribed psychotropic medications at baseline were maintained as needed. Patients underwent their second [^{18}F]DOPA PET scans, two weeks after the completion of antipsychotic discontinuation; their [^{11}C]raclopride PET scans were conducted a week after the second [^{18}F]DOPA PET. To ascertain the washout of antipsychotic drugs, blood samples for the measurement of antipsychotic plasma concentrations were obtained when [^{11}C]raclopride PET scans were conducted. Patients were followed up for 12 weeks after the completion of antipsychotic discontinuation to assess their clinical symptoms and to determine if they experienced a psychotic relapse. The follow-up duration of 12 weeks after antipsychotic discontinuation was determined based on prior observations that a large excess of relapse risk arose within 3 months after discontinuing antipsychotic treatment, compared with continued antipsychotic treatment [30, 31]; this indicated that any psychotic relapse during that period was most likely to be caused by antipsychotic discontinuation, rather than other psychosocial factors. Clinical assessment included the following rating scales: PANSS, Brief Psychiatric Rating Scale (BPRS), Young Mania Rating Scale (YMRS), and Hamilton Depression Rating Scale (HAMD). Demographic data were obtained including age, sex, years of education, duration of illness, antipsychotic medication, its chlorpromazine equivalent dose calculated based on the formula from Andreasen et al. [32], duration of antipsychotic medication, handedness determined by using Annett Hand Preference Questionnaire [33], and smoking status. A psychotic relapse was defined as follows: (1) patients who had any item with a score ≥5 on the positive subscale of the PANSS; (2) those who showed 20% or more increase in PANSS total score from the baseline; (3) those who needed hospitalization for psychotic symptom worsening, suicidality and/or violence; or (4) those who required re-introduction of antipsychotic treatment at the clinicians' decision. The psychotic relapses were determined by a clinician who was blind to the results of the PET studies.

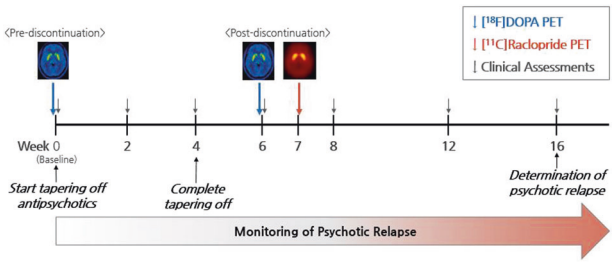


Fig. 1 Diagram illustrating the study design. The blue and red arrow each marks the point the time of [^{18}F]DOPA PET and [^{11}C]raclopride PET. The black arrows are the point of the clinical assessments.

Healthy controls also received two [^{18}F]DOPA PET scans and one [^{11}C]raclopride PET scan at times corresponding to scans of the patients (Fig. 1).

The sample size was calculated based on reports regarding differences in presynaptic dopamine activity

between antipsychotic-responsive psychotic patients and healthy controls [7], under the assumption that persistent dopamine dysregulation in the present study might be similar to one observed in the patients above. Based on the effect size >1.3 from the observation by Demjaha et al. [7], at least 10 participants in each group were required for the study to have sufficient power (>0.8) to detect persistent presynaptic dopamine abnormality in FEP, compared with healthy controls. Given that the risk of psychotic relapse at 3 months was 39% [30], more than 25 FEP were required for this study.

PET scanning procedure

The PET scans were performed at 6 pm (±2 h) on a Biograph 40 Truepoint PET/CT scanner (Siemens, Knoxville, Tennessee, USA) and participants were required to fast for at least 7 h and abstain from smoking and drinking from midnight prior to the scan. Before the acquisition of the dynamic scans, a short computed tomography was performed for attenuation correction.

For [^{18}F]DOPA PET, participants received 150 mg carbidopa and 400 mg entacapone orally 1 h before scanning to reduce the formation of radiolabeled metabolites [34]. The emission scans were performed over 95 min, following an intravenous bolus injection of approximately 370 MBq of [^{18}F]DOPA. After proceeding with routine corrections for uniformity, decay, and attenuation, the PET imaging data acquired in a list mode were reconstructed with a filtered back-projection followed by a three-dimensional Gaussian filter with 5 mm full-width half-maximum (FWHM). Images were collected in a three-dimensional mode with 148 axial slices, an image size of 256 × 256, a pixel size of 1.34 × 1.34 mm^2 and a slice thickness of 1.5 mm. The dynamic volumetric images were sequenced using the following framing: 2 × 30, 4 × 60, 3 × 120, 3 × 180, and 15 × 300 s.

For [^{11}C]raclopride PET, the emission scans were conducted over 90 min, following a bolus injection of approximately 555 MBq [^{11}C]raclopride. The dynamic volumetric images were acquired with the following framing: 8 × 15, 16 × 30, 10 × 60, 10 × 240 and 6 × 300 s. The correction methods, reconstruction parameters and voxel size were identical to those used for [^{18}F]DOPA PET acquisition.

Image analysis

Kinetic analysis for [^{18}F]DOPA

[^{18}F]DOPA PET image analysis was conducted as previously described [8, 35]. Inter-frame correction for head movement during the scan was performed by denoising the non-attenuation-corrected dynamic images using a level 2, order 64 Battle-Lemarie wavelet filter. Frames were realigned to a single "reference" frame, acquired 8 min post-injection, employing a mutual information algorithm [34]. The transformation parameters were then applied to the corresponding attenuated-corrected dynamic images, creating a movement-corrected dynamic image. Subsequently, the [^{18}F]DOPA template created in a previous study was spatially normalized to the summed image and therefore to the realigned dynamic images [19]. The same transformation was applied to the striatal atlas to define region-of-interest (ROI) in the individual PET data. ROI time-activity curves (TACs) were extracted for the whole striatum, as well as its associative, limbic, and sensorimotor subregions [36]. The cerebellum was used as the reference region as it is a region with minimal dopaminergic projections [36, 37]. The region was derived from the Hammersmith atlas [38], eroded to minimize potential signal contamination from adjacent brainstem and occipital cortex. Finally, using the cerebellar TAC as a reference region input, the Gjedde-Patlak plot [39] was applied at ROI level to derive the influx rate constants (K_i^{cer} (1/min)) relative to the cerebellum. The analysis was performed using a combination of SPM5 package(http://www.fil.ion.ucl.ac.uk/spm) and an in-house code based on Matlab2012b® (The Mathworks Inc., MA, USA). A previous test-retest study has found this approach to have high reliability for the striatum with intraclass correlation coefficients exceeding 0.8 [40].

The main outputs from image analysis underwent manual quality control (QC) by an experienced PET modeler who was blinded to the clinical information. Specifically, we ensured that [^{18}F]DOPA template and anatomical atlases were aligned to individual PET summed images; PET frames were realigned to the same space correcting for subject inter-frame motion; fitting of the brain Patlak plot provided by kinetic modeling was physiological (range from 0 to 0.025 (1/min)); and coefficients of variation (CV) for K_i^{cer} estimates were lower than 20% for each ROIs. Scans that failed any aspect of QC were considered QC failures and excluded from the analysis. ROIs with CV for $K_i^{cer} > 20\%$ were excluded from the analysis.

Kinetic analysis for [^{11}C]raclopride

The summed images of [^{18}F]DOPA and [^{11}C]raclopride from each subject were co-registered; the parameters acquired in the co-registration algorithm were applied to dynamic images of [^{11}C]raclopride. After co-registration, [^{11}C]raclopride images were normalized using the same

parameters obtained during normalization of [^{18}F]DOPA images. TACs for the whole striatum, as well as its associative, limbic, and sensorimotor subregions, were extracted using the above atlas [36].

The simplified reference tissue model was used for kinetic analysis of the [^{11}C]raclopride binding to the dopamine D2/3 receptor, to compute the tracer binding potential (BP_{ND}) to dopamine D2/3 receptors in the striatum [41, 42].

Statistical analysis

Independent t tests and Pearson's χ^2 tests were used to compare demographic variables between groups. A mixed effects model was employed in a repeated measures analysis to test a group effect on K_i^{cer} and BP_{ND} and the effect of an interaction between group and time on K_i^{cer} value. The group (Group: modeled as a categorical variable: 1 = healthy controls, 2 = patients without relapse, 3 = patients with relapse) and the time point of PET imaging were incorporated into the model as fixed effects, and subjects were modeled as random effects. To test the correlation between K_i^{cer} values obtained in healthy controls at week 0 and week 6, we employed intraclass correlation coefficient using a one-way analysis of variance with random subject effects. Pearson's correlation analysis was used to investigate the relationship between K_i^{cer} before the antipsychotic discontinuation and the time to the relapse. Multiple comparison was corrected by using the Bonferroni method.

Results

Demographic and clinical characteristics

Twenty five FEP and fourteen healthy controls were enrolled in the study. Table 1 shows the demographic characteristics of the participants. The mean [SD] age was younger in healthy controls (22.6 [2.9]) than FEP (26.4 [6.3]) ($t = -2.120$, df = 37, $p = 0.041$). There were no significant differences in other demographic characteristics including sex ratio ($\chi^2 = 2.345$, df = 1, $p = 0.126$), handedness ($\chi^2 = 5.414$, df = 2, $p = 0.067$), years of education ($t = -0.215$, df = 37, $p = 0.831$), and smoking status ($\chi^2 = 0.613$, df = 1, $p = 0.434$) between healthy controls and patients. Diagnoses of FEP included schizophrenia ($N = 20$), major depressive disorder ($N = 3$), schizoaffective disorder ($N = 2$), delusional disorder ($N = 2$), and bipolar disorder ($N = 1$). All patients diagnosed with major depressive disorder had a depressive episode prior to the first psychotic episode and were diagnosed with schizophrenia afterwards.

Psychotic relapse after antipsychotic discontinuation

Within 12 weeks after the completion of antipsychotic discontinuation, 10 of 25 patients (40%) met criteria for a psychotic relapse. Among the criteria defined in the study design section, the first criterion was met for one FEP, the second for two FEP, the third for one FEP, and the fourth for six FEP. There were no significant differences in baseline demographic characteristics including age ($t = 0.536$, df = 23, $p = 0.597$), sex ratio ($\chi^2 = 0.031$, df = 1, $p = 0.861$), handedness ($\chi^2 = 0.198$, df = 2, $p = 0.906$), years of education ($t = -1.082$, df = 23, $p = 0.291$), diagnosis ($\chi^2 = 7.529$, df = 4, $p = 0.110$), duration of illness ($t = -0.940$, df = 23, $p = 0.357$), antipsychotic medication ($\chi^2 = 3.985$, df = 6, $p = 0.679$), duration of antipsychotic treatment ($t = -0.766$, df = 23, $p = 0.452$), chlorpromazine equivalent dose ($t = -0.402$, df = 23, $p = 0.692$), and smoking status ($\chi^2 = 0.063$, df = 1, $p = 0.802$) between patients who relapsed (Relapse) and patients who remained relapse-free (Non-relapse) (Table 1).

The mean [SD] PANSS total score at baseline was 40.6 [11.4], and there was no significant difference between Relapse (41.1 [12.1]) and Non-relapse (40.2 [11.4]) ($t = -0.189$, df = 23, $p = 0.852$). However, the change in the PANSS total score differed according to the relapse status (Week*Group: $F = 12.882$, df = 2,65, $p < 0.001$); there was a significant increase in PANSS total score in Relapse, compared with no change in Non-relapse (Fig. 2).

Striatal dopamine synthesis capacity

Twenty five patients and fourteen healthy controls underwent [^{18}F]DOPA PET scans. The mean [SD] injected dose of [^{18}F]DOPA was 358.9 [18.5] MBq in healthy controls, 358.9 [37.0] MBq in Non-relapse and 362.6 [25.9] MBq in Relapse. There were no significant differences in injected dose among the three groups ($F = 0.170$, df = 2,74, $p = 0.865$). Two sets of healthy control data from [^{18}F]DOPA PET scans were excluded from the analysis due to QC failure. The mean [SD] K_i^{cer} values in the striatum were as follows: 0.0131 [0.0008] in healthy controls, 0.0130 [0.0012] in Relapse and 0.0132 [0.0012] in Non-relapse at week 0; 0.0133 [0.0013] in healthy controls, 0.0134 [0.0006] in Relapse and 0.0129 [0.0014] in Non-relapse at week 6. The intraclass coefficient of K_i^{cer} values obtained in healthy controls at week 0 and week 6 was 0.695 ($p < 0.001$). The K_i^{cer} values in the striatum measured at baseline (week 0) and at week 6 were not significantly different between two groups including FEP and healthy controls (Week: $F = 0.148$, df = 1,412.5, $p = 0.700$; Group: $F = 0.145$, df = 1,36.564, $p = 0.706$; Week*Group: $F = 2.429$, df = 1,412.520, $p = 0.120$). However, when FEP were

Table 1 Baseline demographic and clinical characteristics of participants.

	Healthy controls	Patients with psychotic disorders					Statistics	*p* value
		Non-relapse	Relapse	Statistics	*p* value	Total		
	($n = 14$)	($n = 15$)	($n = 10$)			($n = 25$)		
Age (year)[a]	22.6 ± 2.9	27.0 ± 7.0	25.6 ± 5.4	$t = 0.536$, df = 23	0.597	26.4 ± 6.3	$t = -2.120$, df = 37	0.041
Sex (male/female)	8/6	5/10	3/7	$\chi^2 = 0.031$, df = 1	0.861	8/17	$\chi^2 = 2.345$, df = 1	0.126
Height (cm)[a]	168.8 ± 8.0	168.0 ± 10.1	163.4 ± 5.0	$t = 1.358$, df = 23	0.188	166.2 ± 8.6	$t = 0.939$, df = 37	0.354
Weight (kg)[a]	61.6 ± 9.1	68.3 ± 15.3	62.7 ± 8.1	$t = 1.043$, df = 23	0.308	66.1 ± 13.0	$t = -1.142$, df = 37	0.261
Handedness (L/R/B)	5/9/0	1/13/1	1/8/1	$\chi2 = 0.198$, df = 2	0.906	2/21/2	$\chi^2 = 5.414$, df = 2	0.067
Education (year)[a]	15.1 ± 1.8	14.9 ± 1.7	15.8 ± 2.3	$t = -1.082$, df = 23	0.291	15.3 ± 2.0	$t = -0.215$, df = 37	0.831
Diagnosis (n)		Schizophrenia(14) MDD(3)[b] Schizoaffective disorder(1) Delusional disorder(0) Bipolar disorder(0)	Schizophrenia(6) MDD(0) Schizoaffective disorder(1) Delusional disorder(2) Bipolar disorder(1)	$\chi^2 = 7.529$, df = 4	0.110	Schizophrenia(20) MDD(3)[b] Schizoaffective disorder(2) Delusional disorder(2) Bipolar disorder(1)		
Duration of Illness (month)[a]		34.3 ± 21.3	45.6 ± 38.7	$t = -0.940$, df = 23	0.357	38.8 ± 29.3		
Antipsychotic medications (n)		Aripiprazole(5) Amisulpride(3) Blonanserin(2) Olanzapine(1) Paliperidone(2) Quetiapine(1) Risperidone(4)	Aripiprazole(3) Amisulpride(4) Blonanserin(0) Olanzapine(1) Paliperidone(2) Quetiapine(0) Risperidone(1)	$\chi^2 = 3.985$, df = 6	0.679	Aripiprazole(8) Amisulpride(7) Blonanserin(2) Olanzapine(2) Paliperidone(4) Quetiapine(1) Risperidone(5)		
Duration of Antipsychotic Treatment (month)[a]		28.3 ± 20.9	37.0 ± 36.2	$t = -0.766$, df = 23	0.452	31.8 ± 27.7		
Chlorpromazine equivalent dose (mg)[a]		252.6 ± 124.4	275.9 ± 165.8	$t = -0.402$, df = 23	0.692	261.9 ± 139.5		
Concomitant medications (n)		None(4) Benzodiazepine(7) Antiparkinsonian agent(9) SSRI(0)Mood stabilizer(1)	None(1) Benzodiazepine(7) Antiparkinsonian agent(6) SSRI(2)Mood stabilizer(0)	$\chi^2 = 4.812$, df = 4	0.307	None(5) Benzodiazepine(14) Antiparkinsonian agent(15) SSRI(2)Mood stabilizer(1)		
Cigarette smoker (n)	3	2	1	$\chi^2 = 0.063$, df = 1	0.802	3	$\chi^2 = 0.613$, df = 1	0.434
PANSS score[a]								
Total		40.2 ± 11.4	41.1 ± 12.1	$t = -0.189$, df = 23	0.852	40.6 ± 11.4		
Positive		8.5 ± 2.7	9.0 ± 2.2	$t = -0.512$, df = 23	0.614	8.7 ± 2.5		
Negative		10.0 ± 3.8	9.7 ± 4.1	$t = 0.189$, df = 23	0.851	9.9 ± 3.8		
General		21.7 ± 6.3	22.4 ± 6.8	$t = -0.252$, df = 23	0.804	22.0 ± 6.4		
BPRS score[a]		30.9 ± 7.1	31.0 ± 6.4	$t = -0.048$, df = 23	0.962	30.9 ± 6.7		
YMRS score[a]		1.3 ± 2.7	1.4 ± 2.3	$t = -0.064$, df = 23	0.950	1.4 ± 2.5		
HAMD score[a]		3.4 ± 2.6	4.4 ± 3.0	$t = -0.896$, df = 23	0.380	3.8 ± 2.7		

Baseline differences in demographic and clinical characteristics were analyzed using unpaired t tests for continuous variables and Fisher exact test for categorical variables.

BPRS Brief Psychiatric Rating Scale, *MDD* major depressive disorder, *HAMD* Hamilton Depression Rating Scale, *PANSS* Positive and Negative Syndrome Scale, *SSRI* selective serotonin reuptake inhibitor, *YMRS* Young Mania Rating Scale.

[a]The values are presented as mean ± standard deviation.

[b]All patients diagnosed with major depressive disorder had a depressive episode prior to the first psychotic episode and were diagnosed with schizophrenia afterwards.

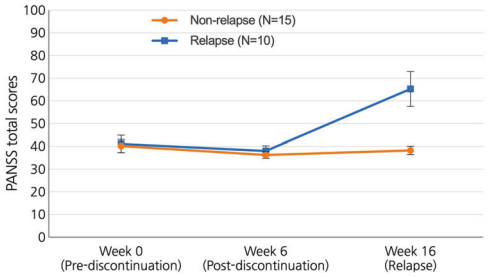


Fig. 2 The PANSS total scores according to patient relapse statuses. There was a significant interaction between group and week. Error bars indicate standard errors of the mean. The mean and the standard error were estimated from a mixed effects model (Week: $F = 0.605$, df = 2,65, $p = 0.546$; Group: $F = 0.039$, df = 1,65, $p = 0.842$; Week*Group: $F = 12.882$, df = 2,65, $p < 0.001$).

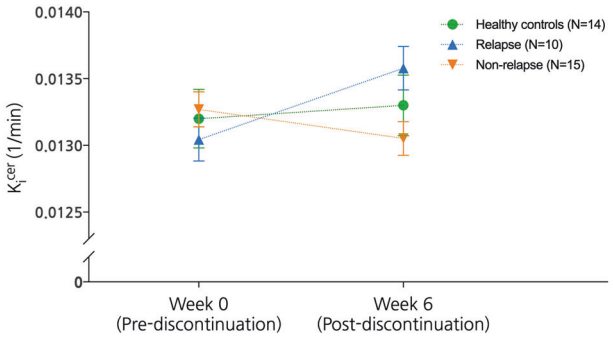


Fig. 3 Changes in K_i^{cer} values in patients with first-episode psychosis (FEP) and healthy controls. Relapse represents FEP who showed psychotic relapse within 12 weeks after antipsychotic discontinuation, while Non-relapse includes FEP who did not exhibit psychotic relapse within 12 weeks after antipsychotic discontinuation. Error bars indicate standard errors of the mean. The mean and the standard error were estimated from a mixed effects model. There was a significant interaction between group and week (Week: $F = 0.577$, df = 1,253.681, $p = 0.448$; Group: $F = 0.064$, df = 2,78.395, $p = 0.938$; Week*Group: $F = 4.827$, df = 2,253.193, $p = 0.009$).

divided into Relapse and Non-relapse, there was a significant group-by-time effect on change in the K_i^{cer} values between Relapse, Non-relapse and healthy controls (Week*Group: $F = 4.827$, df = 2,253.193, $p = 0.009$) (Fig. 3). The K_i^{cer} values were not significantly different at baseline (week 0) ($F = 0.467$, df = 2,211.080, $p = 0.628$), but they were significantly different at week 6 ($F = 3.512$, df = 2,202.165, $p = 0.032$) between Relapse, Non-relapse and healthy controls. Pairwise comparison of the K_i^{cer} values at week 6 using multiple comparison correction revealed significant differences between Relapse and Non-relapse ($p = 0.043$) and between healthy controls and Non-relapse ($p = 0.019$), but not between Relapse and healthy controls ($p = 0.854$). Post hoc analyses found significant group-by-time interactions when comparing Relapse with Non-relapse, as well as Non-relapse with healthy controls (Relapse vs. Non-relapse: Week*Group: $F = 5.692$, df = 1,181.886, $p = 0.018$; Relapse vs. Healthy controls: Week*Group: $F = 0.061$, df = 1,137.015, $p = 0.806$; Non-relapse vs. Healthy controls: Week*Group: $F = 7.721$, df = 1,187.700, $p = 0.006$). Multiple comparison correction showed similar results (Relapse vs. Non-relapse: $p = 0.054$; Relapse vs. Healthy controls: $p = 1.000$; Non-relapse vs. Healthy controls: $p = 0.018$). Group-wise comparison to explore difference in K_i^{cer} values between week 0 and week 6 was conducted and there was significant difference in Non-relapse ($F = 12.362$, df = 1,110.641, $p = 0.001$), but neither in Relapse ($F = 0.058$, df = 1,70.943, $p = 0.810$) nor in healthy controls ($F = 1.371$, df = 1,71.096, $p = 0.246$). The group-wise comparison was still significant in Non-relapse after multiple comparison correction (Non-relapse: $p = 0.003$; Relapse: $p = 1.000$; Healthy control: $p = 0.738$).

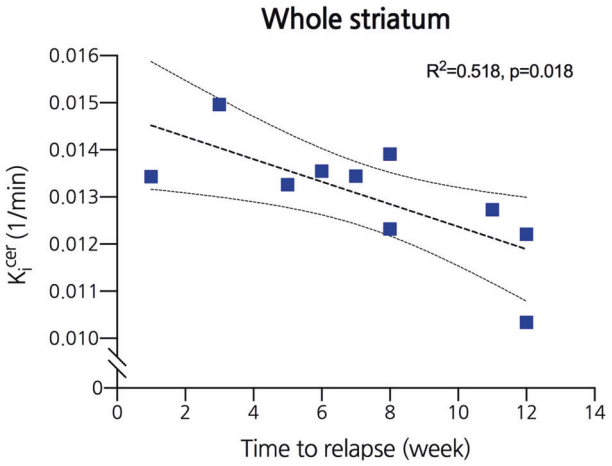
Furthermore, a significant group-by-time interaction effect on the K_i^{cer} values of Relapse and Non-relapse was found in the associative subdivision, but not in the limbic or sensorimotor subdivisions (Associative striatum: Week*Group: $F = 4.257$, df = 1,131.033, $p = 0.041$; Limbic striatum: Week*Group: $F = 2.478$, df = 1,173.031, $p = 0.117$; Sensorimotor striatum: Week*Group: $F = 3.034$, df = 1,119.999, $p = 0.084$). However, the results did not remain significant after multiple comparison correction (Associative striatum: $p = 0.123$; Limbic striatum: $p = 0.351$; Sensorimotor striatum: $p = 0.252$).

In the Relapse group, a significant negative correlation was found between baseline (week 0) striatal K_i^{cer} values and relapse-free period after antipsychotic discontinuation ($R^2 = 0.518$, $p = 0.018$) (Fig. 4). Notably, in subdivision analysis, a significant correlation was found in the associative striatum, but not in the limbic or sensorimotor striatum (Associative striatum: $R^2 = 0.625$, $p = 0.006$; Limbic striatum: $R^2 = 0.389$, $p = 0.054$; Sensorimotor striatum: $R^2 = 0.267$, $p = 0.126$). Multiple comparison correction showed the same result (Associative striatum: $p = 0.018$; Limbic striatum: $p = 0.162$; Sensorimotor striatum: $p = 0.378$). However, no significant correlations were found between the striatal K_i^{cer} values measured at week 6 and relapse-free period ($R^2 = 0.201$, $p = 0.226$).

Striatal dopamine D2/3 binding potential

[^{11}C]raclopride PET scan was conducted in 23 patients (Relapse = 8, Non-relapse=15) and 12 healthy controls. The mean [SD] injected dose of [^{11}C]raclopride was 532.8 [51.8] MBq in healthy controls, 536.5 [66.6] MBq in Non-relapse, and 499.5 [103.6] MBq in Relapse. There were no differences in the injected dose among groups ($F = 0.800$, df = 2,32, $p = 0.459$). Plasma levels of antipsychotic drugs measured just before the [^{11}C]raclopride PET scan were not detectable in any patients. The mean [SD] BP_{ND} in the

a. Whole striatum



b. Associative striatum

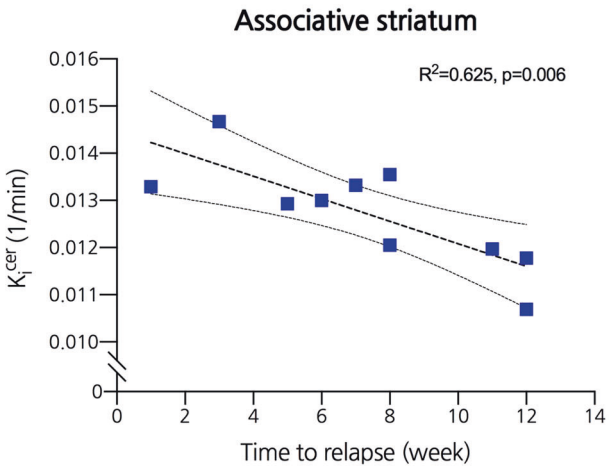


Fig. 4 Relationship between K_i^{cer} values at baseline and the time taken to psychotic relapse after antipsychotic discontinuation in patients with first-episode psychosis. a Describes the relationship between K_i^{cer} values of whole striatum and time to relapse. **b** Describes the relationship between K_i^{cer} values of associative striatum and time to relapse.

striatum was 2.6 [0.1] in healthy controls, 2.5 [0.5] in Relapse and 2.7 [0.2] in Non-relapse. No significant differences were observed in [^{11}C]raclopride BP_{ND} among healthy controls, Relapse and Non-relapse ($F = 1.402$, df = 2,32.000, $p = 0.261$).

Subgroup analysis in schizophrenia

We conducted the same analysis in the group of patients with schizophrenia. There was also a significant group-by-time effect on change in the K_i^{cer} values between Relapse, Non-relapse and healthy controls (Week*Group: $F = 9.853$, df = 2,221.261, $p < 0.001$). Significant group-by-time interactions were also found when comparing Relapse with Non-relapse, as well as Non-relapse with healthy controls (Relapse vs. Non-relapse: Week*Group: $F = 21.463$, df = 1,139.658, $p < 0.001$; Relapse vs. Healthy controls: Week*Group: $F = 1.163$, df = 1,99.384, $p = 0.283$; Non-relapse vs. Healthy controls: Week*Group: $F = 11.441$, df = 1,160.856, $p = 0.001$). Multiple comparison correction showed the same results (Relapse vs. Non-relapse: $p < 0.001$; Relapse vs. Healthy controls: $p = 0.849$; Non-relapse vs. Healthy controls: $p = 0.003$). Group-wise comparison to explore difference in K_i^{cer} values between week 0 and week 6 found significant differences in Non-relapse ($F = 26.856$, df = 1,97.412, $p < 0.001$) and in Relapse ($F = 4.954$, df = 1,40.879, $p = 0.032$), but not in healthy controls ($F = 1.338$, df = 1,62.916, $p = 0.252$). The group-wise comparison was still significant in Non-relapse after multiple comparison correction (Non-relapse: $p < 0.001$; Relapse: $p = 0.096$; Healthy control: $p = 0.756$).

The correlation between baseline (week 0) striatal K_i^{cer} values and relapse-free period after antipsychotic discontinuation in Relapse did not reach statistical significance ($R^2 = 0.526$, $p = 0.102$). [^{11}C]raclopride BP_{ND} was not significant different among healthy controls, Relapse and Non-relapse ($F = 2.201$, df = 2,44.626, $p = 0.123$).

Discussion

Our study found that the longitudinal change in striatal dopamine synthesis capacity differed depending on whether patients showed a psychotic relapse within 12 weeks after discontinuing antipsychotic treatment. Furthermore, dopamine synthesis capacity measured before antipsychotic discontinuation showed a significant negative correlation with time to psychotic relapse after antipsychotic discontinuation, indicating that higher dopamine synthesis capacity before antipsychotic discontinuation was associated with a shorter time to psychotic relapse. These results were consistently found in the subgroup analysis with schizophrenia. To the best of our knowledge, this is the first prospective study to evaluate the dopaminergic system in relation to psychotic relapse after antipsychotic discontinuation in FEP.

We tested whether a persistent elevation of presynaptic dopamine activity was related to psychotic relapse after antipsychotic discontinuation (Hypothesis 1). However, there were no differences in K_i^{cer} values among Relapse, Non-Relapse and healthy controls. This finding contrasts with the results of previous radiolabeled DOPA PET studies in patients with schizophrenia, which revealed an elevation of presynaptic dopamine synthesis capacity in affected patients (See Table 3 in Kim et al.) [4, 8]. Neither Relapse

nor Non-Relapse showed elevated dopamine synthesis capacity. This finding might be associated with a state effect of antipsychotic treatment in FEP [21, 43–45]. All studies conducted in drug-naïve or drug-free patients using radiolabeled DOPA consistently reported higher levels of presynaptic dopamine activity in patients with psychotic disorders, compared with healthy controls [46–53]. In contrast, psychotic patients treated with antipsychotic drugs showed inconsistent levels of presynaptic dopamine activity. To our knowledge, eight studies have investigated dopamine synthesis capacity in patients treated with antipsychotic drugs [7, 8, 19, 54–58]. Three studies found higher levels of presynaptic dopamine activity in patients [19, 56, 57], whereas two studies reported no differences between patients treated with antipsychotic drugs and healthy controls [54, 55], and one study showed lower levels in patients in symptomatic remission under antipsychotic medication [58]. Kim et al. [8] reported no difference in first-line antipsychotic responders and lower levels of presynaptic dopamine function in patients treated with clozapine, while Demjaha et al. [7] demonstrated higher levels of presynaptic dopamine function in antipsychotic responders and no difference in antipsychotic-refractory patients. The inconsistent results might be attributed to time-dependent inactivation of dopamine neuron firing by antipsychotic drugs, as shown in animal studies [43, 44]. In addition, the antipsychotic effect on dopamine neuron firing might be related to the observation that subchronic haloperidol downregulated dopamine synthesis capacity in patients with schizophrenia [21]. However, a long-term prospective study is still needed to confirm the antipsychotic effect on the dopamine synthesis capacity in humans.

Although the presynaptic dopamine synthesis did not differ before the antipsychotic discontinuation, the change in the K_i^{cer} after the discontinuation was significantly different according to relapse status (Hypothesis 2). Notably, different changes were observed before worsening of psychotic symptoms (Figs. 2 and 3). We expected that the presynaptic dopamine synthesis capacity would increase after antipsychotic discontinuation in patients who relapsed during the 12-week follow-up period. However, from a statistical perspective, the significant difference was driven by the reduction in K_i^{cer} of patients in Non-relapse. All antipsychotic drugs are dopamine blockers, which reduce dopaminergic neurotransmission from the presynaptic area by occupying postsynaptic receptors [59–61]. Thus, the antipsychotic discontinuation may increase dopaminergic neurotransmission to the postsynaptic area, where autoregulation of dopamine synthesis capacity is necessary to stabilize dopaminergic neurotransmission. Indeed, the activity of aromatic amino acid decarboxylase (AAADC), which decarboxylates [^{18}F]DOPA, was reported to be reduced by dopamine agonist and increased by dopamine antagonist in an animal study [62]. Furthermore, increased dopamine synthesis capacity after haloperidol administration were observed in healthy controls [45]. These observations in both animals and humans demonstrate the regulation of AAADC activity by change in dopaminergic neurotransmission to the postsynaptic area. In this context, the reduction in K_i^{cer} values observed in Non-Relapse can be interpreted as the consequence of a normal regulatory effect on dopamine synthesis capacity by the negative feedback mechanism [62–64]. In contrast, Relapse didn't exhibit a reduction in K_i^{cer} values; moreover, the level of presynaptic dopamine synthesis measured after the antipsychotic discontinuation was higher in Relapse than in Non-Relapse. This suggests dysfunctional autoregulation of dopamine synthesis capacity in Relapse. However, the level of presynaptic dopamine function measured after antipsychotic discontinuation did not significantly differ between Relapse and healthy controls. That may explain why Relapse did not demonstrate symptomatic worsening at Week 6, in terms of PANSS score.

Dysfunctional autoregulation may be related to the progressive increase in dopamine synthesis capacity observed in patients who developed psychosis [24]. We did not measure dopamine synthesis capacity at the point of the relapse in patients. However, one of the patients enrolled in the study had relapsed at the time of the second [^{18}F]DOPA scan. The K_i^{cer} value measured at the time showed a significant increase relative to baseline, which supports the speculation that progressive dopamine dysregulation related to abnormal autoregulation may cause psychotic relapse after antipsychotic discontinuation. We also found a significant negative correlation between striatal K_i^{cer} value and time to the psychotic relapse after antipsychotic discontinuation, as shown in Fig. 4. The larger standard deviation of K_i^{cer} value observed before antipsychotic discontinuation in FEP compared to HC group, which is consistent with a prior report [65] indicating biological heterogeneity in FEP group, might influence the correlation as well as the group-by-time interaction above. The correlation was found to be even stronger in the associative striatum, which is regarded as a major locus of dopaminergic dysfunction in psychotic disorders [20, 66, 67]. This implies that higher presynaptic dopamine synthesis capacity before discontinuation of antipsychotic treatment may be associated with more rapid psychotic exacerbation after antipsychotic discontinuation in patients who relapse. Higher levels of dopamine synthesis capacity could reflect reduced stability of the dopamine system, as observed in subjects at high risk for psychosis who exhibited higher levels of presynaptic dopamine activity compared with healthy controls, however, these higher levels in subjects at high risk for psychosis were lower than the levels in patients

with schizophrenia [53]. Reduced stability and discontinuation of antipsychotic drugs may have led to rapid psychotic relapse.

We tested whether dopamine D2/3 receptor upregulation may underlie psychotic relapse (Hypothesis 3). For this assessment, we measured dopamine D2/3 receptor availability after antipsychotic discontinuation and investigated differences according to relapse status. We found no differences in dopamine D2/3 receptor availability among the healthy controls, Relapse and Non-relapse. However, we could not exclude the possibility of a difference in dopamine D2/3 receptor availability before the antipsychotic discontinuation, because patients had not been taking antipsychotic medication for at least 3 weeks when [^{11}C] raclopride PET was conducted. During this period, receptor availability may have normalized. Also, the affinity state of dopamine D2/3 receptor, which has been proposed to be related with dopamine hypersensitivity [26], might have some effect as well. Moreover, the [^{11}C]raclopride is known to be sensitive to the change in endogenous dopamine [68], and the endogenous dopamine level might be different between groups after antipsychotic discontinuation as seen in different K_i^{cer} values. Since BP_{ND} was measured only once, the implication of endogenous dopamine level on the dopamine D2/3 receptor availability cannot be disregarded. In addition, the sample size was determined with a focus on presynaptic dopamine capacity. Because the effect size for an increase in receptor availability in patients with schizophrenia was reported to be smaller ($d = 0.26$) than the effect size for presynaptic dopamine capacity ($d = 0.79$) [4], the absence of a difference in receptor availability could reflect limited statistical power. Nonetheless, the absence of altered dopamine D2/3 receptor availability in FEP is consistent with previous results from drug-naïve patients [69, 70].

Limitations

This study had some limitations that need to be considered when interpreting and applying the results. Patients with FEP in this study were taking various antipsychotic medications during baseline assessment. This could have affected dopamine synthesis capacity at baseline and time to psychotic relapse.

Because of the study design, dopamine synthesis capacity was not measured at the time of relapse in patients. Therefore, the observed trend indicating a change in dopamine synthesis capacity after antipsychotic discontinuation may not reflect the entire course of disease progression before relapse.

In accordance with the inclusion/exclusion criteria, individuals with a history of substance abuse or dependence were excluded. However, three patients and three healthy controls were current smokers. There are some reports that cigarette smoking can influence dopamine synthesis capacity, although the results are inconsistent [71–73]. Nonetheless, smoking was prohibited, beginning at midnight prior to the scan, and the proportion of smokers did not significantly differ between groups. Therefore, smoking is unlikely to have affected the results.

Finally, the results were based on relapse outcome within 12 weeks after antipsychotic discontinuation. Although dopaminergic dysfunction is considered the most probable mechanism underlying psychotic relapse after antipsychotic discontinuation, the effects of environmental factors (e.g., psychosocial stress) on psychotic relapse are undeniable [74]. The determination of psychotic relapse shortly after antipsychotic discontinuation might have minimized the confounding effects of other environmental factors on psychotic relapse, but restricts the generalizability of the results.

Conclusion

Change in dopamine synthesis capacity after antipsychotic discontinuation was related to psychotic relapse in patients with FEP, but dopamine D2/3 receptor availability was not related to relapse. These results suggest that dysfunctional dopamine autoregulation might precipitate psychotic relapse after antipsychotic discontinuation in FEP. This provides a neurobiological understanding of psychotic relapse after antipsychotic discontinuation and could be used to develop a strategy for prevention of psychotic relapse related to antipsychotic discontinuation.

Acknowledgements This work was supported by the National Research Foundation of Korea(NRF) grants funded by the Korea government(MSIT) (No. NRF-2019R1A2C2005500, NRF-2019M3C7A1032472)

Compliance with ethical standards

Conflict of interest Dr Euitae Kim has participated in advisory/speaker meetings organized by Janssen Korea, Otsuka Korea, and Bukwang Pharm Company. Professor. Oliver D. Howes has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organized by Angellini, Astra-Zeneca, Autifony, Biogen, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Sunovion, Rand, Recordati, and Roche. Professor Jun Soo Kwon has received honorarium from Bukwang Pharm Company, Pfizer Korea, Ostuka Korea and participated in advisory meetings for Boehringer Ingelheim. Professor Jun Soo Kwon was the principal investigator of research projects from Otsuka company and Janssen Korea. The other authors have nothing to declare. Neither authors nor their families have been employed by or have holdings/a financial stake in any biomedical company.

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