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ORIGINAL INVESTIGATION

The relationship between antipsychotic D_2 occupancy and change in frontal metabolism and working memory

A dual [^{11}C]raclopride and [^{18}F]FDG imaging study with aripiprazole

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Abstract
Rationale The effects of aripiprazole on cognitive function are obscure, possibly due to the difficulty in disentangling the specific effects on cognitive function from effects secondary to the improvement of other schizophrenic symptoms. This prompts the necessity of using an intermediate biomarker relating the drug effect on the brain to change in cognitive function.
Objectives To explore the effect of aripiprazole on cognitive function, we measured changes in frontal metabolism as an intermediate biomarker and sought to determine its relationship with D_2 receptor occupancy and changes in working memory.
Methods Fifteen healthy male volunteers participated in the study. Serial positron emission tomography (PET) scans with [^{11}C]raclopride and [^{18}F]FDG were conducted 1 day before and 2 days after the administration of aripiprazole. The subjects performed the *N*-back task just after finishing the [^{18}F]FDG scan.
Results The mean (±SD) D_2 receptor occupancies were 22.2 ±16.0 % in the 2 mg group, 35.5±3.6 % in the 5 mg group, 63.2±9.9 % in the 10 mg group and 72.8±2.1 % in the 30 mg group. The frontal metabolism was significantly decreased after the administration of aripiprazole (t=2.705, df=14, p=0.017). Greater striatal D_2 receptor occupancy was related to greater decrease in frontal metabolism (r=−0.659, p=0.010), and greater reduction in frontal metabolism was associated with longer reaction times (r=−0.597, p=0.019) under the greatest task load.
Conclusions Aripiprazole can affect cognitive function and alter frontal metabolic function. The changes in these functions are linked to greater D_2 receptor occupancy. This suggests that it may be important to find the lowest effective dose of aripiprazole in order to prevent adverse cognitive effects.

Keywords Aripiprazole · Working memory · Raclopride C11 · Fluorodeoxyglucose F18 · Positron emission tomography

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Introduction

Aripiprazole acts as a potent partial dopamine D_2 receptor agonist, which is believed to reduce dopaminergic neurotransmission in the mesolimbic pathway, where hyperactivity is thought to underlie psychotic symptoms in schizophrenia, while simultaneously enhancing dopaminergic function in cortical regions, where hypodopaminergia is thought to underlie negative and cognitive symptoms (see review articles by Davis et al. 1991; Howes and Kapur 2009). This unique pharmacological profile might predict efficacy against both cognitive and negative symptoms as well as positive symptoms of schizophrenia.

Indeed, it has been demonstrated to be safe and effective in treating psychotic symptoms in schizophrenia (Kasper et al. 2003; Potkin et al. 2003) and improvements in cognitive function have also been reported in patients receiving aripiprazole (Schlagenhauf et al. 2010; Suzuki et al. 2011). However, its effects on cognitive function are less clear-cut, with some evidence that it can also impair some aspects of cognitive performance (Yasui-Furukori et al. 2012). These discrepant findings with respect to the effects of aripiprazole on cognition could be due to differences between studies in the task parameters used or the baseline performance of subjects and drug occupancy levels in the brain. Furthermore, it is not easy to disentangle the specific effects of aripiprazole on cognitive function from secondary effects due to the improvement of other symptoms in schizophrenia. This prompts the necessity of using an intermediate biomarker relating the drug effect on the brain to change in cognitive function, thereby making it possible to directly explore the effect of antipsychotic drugs on cognitive function.

It has been reported that antipsychotics, including aripiprazole, induce metabolic decreases in the frontal lobe (Bartlett et al. 1998; Kim et al. 2008; Lane et al. 2004; Molina et al. 2003, 2005b) that are related to cognitive function such as working memory (Barch and Smith 2008; Owen et al. 2005). As brain regional metabolism primarily reflects neuronal activity within the region (Magistretti and Pellerin 1996, 1999), the brain metabolic change by antipsychotics can be largely attributed to altered neuronal activity in a given region. Thus the frontal metabolic decrease suggests that antipsychotics are reducing neuronal activity, which in turn is likely to underlie the effects of antipsychotics on cognitive function. This implies that frontal metabolic change induced by antipsychotics could be a useful intermediate biomarker for investigating antipsychotic effects on cognitive function.

The mechanism that mediates the antipsychotic effect on frontal metabolism and cognitive function is not fully understood, but several lines of evidence suggest it could be secondary to D_2 receptor blockade. Firstly, despite their widely varying pharmacology, all antipsychotics block D_2 receptors (Howes et al. 2009a). Secondly, animal studies show that cognitive function is closely linked to dopaminergic activity in the frontal cortex (Castner et al. 2004; Goldman-Rakic et al. 2004). However, there is also evidence from transgenic mice that even relatively small alterations in D_2 receptor availability in the striatum can lead to cognitive impairments in tasks thought to be subserved by the frontal cortex (Simpson et al. 2010). Thus D_2 receptor occupancy either in the frontal cortex or in the striatum may alter frontal metabolism and cognitive functions that involve the frontal cortex.

However, it is also possible that the cognitive and metabolic effects of antipsychotics are due to their actions at other receptor systems, in particular the serotonin (5-HT) system. The serotonin system also mediates cognitive functions. Animal studies have generally shown that 5-HT_{2A} antagonists impair some aspects of cognitive function, although the effect of 5-HT_{1A} agonism on cognition is still debatable (Keefe et al. 1999). Aripiprazole has high affinities for 5-HT_{1A} and 5-HT_{2A} receptors and acts as a partial 5-HT_{1A} agonist and 5-HT_{2A} antagonist (Hirose and Kikuchi 2005). Thus cognitive effects due to aripiprazole could be mediated by its serotonergic effects as well as its dopaminergic effects. Although the role of 5-HT in cognition is significant, for the purpose of this study, we decided to constrain our inquiry to the dopamine system by focusing on one aspect of cognitive function — working memory — that is known to be closely associated with dopaminergic activity (Barch and Smith 2008).

Thus, to examine the effect of aripiprazole on cognitive function, we sought to determine the relationship between D_2 receptor occupancy and changes in frontal metabolism and working memory. D_2 receptor occupancy would inform us about the pharmacokinetics of aripiprazole in the brain and the change in frontal metabolism would enable to track the drug effect on the brain as a pharmacodynamics parameter. For this, we measured dopamine receptor occupancy and frontal metabolic change in healthy volunteers using [^{11}C]raclopride and [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) after the administration of aripiprazole. At the same time, we related the frontal metabolic change to the performance on working memory.

Materials and methods

The present study was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, South Korea, and was carried out in accordance with the Declaration of Helsinki.

Subjects

Fifteen right-handed, non-smoking, healthy male volunteers participated in the study. After complete description of the study to the subjects, written informed consent was obtained.

Screening tests for healthy volunteers included physical examination, vital signs, laboratory tests (hematology, blood chemistry, and urinalysis), and a 12-lead electrocardiograms. A psychiatric interview with the Structured Clinical Interview for DSM-IV-TR Axis I disorders, Research Version, Non-patient Edition (SCID-I/NP) (First et al. 2002) was conducted. Subjects with any medically significant abnormality on investigations and/or psychiatric disease were excluded. We previously reported that the Taq1A polymorphism in the dopamine D_2 receptor gene affects brain metabolic response to aripiprazole, such that greater frontal metabolic change was observed with the A2A2 genotype (Kim et al. 2008). Thus we selected subjects with the A2A2 genotype to obtain a homogeneous study sample. Mean (±SD) age, height and body weight of the healthy volunteer group was 23.1±2.4 years, 174.5±5.0 cm and 69.9±6.7 kg, respectively.

Study design

The study followed a single-blind, single oral parallel dose group design (Fig. 1). The dose of aripiprazole was 2 mg for three subjects, 5 mg for four subjects, 10 mg for four subjects and 30 mg for four subjects. The doses were selected to give a wide range of receptor occupancies based on published data on dopamine receptor occupancy by aripiprazole (Kegeles et al. 2008).

Subjects were required to stay at the Clinical Trial Centre, Seoul National University Hospital and to abstain from caffeine or caffeine-containing products (e.g., coffee, cola, black tea, green tea, chocolate), grapefruit-containing products, alcohol and smoking for the duration of study. After fasting for at least 4 h, the subjects received the randomly assigned single oral dose of aripiprazole, with 240 ml water, at 12:30 p.m.

The PET scans for the measurement of dopamine receptor occupancy and brain metabolic change were done 1 day before and 2 days after the administration of aripiprazole. The effect of aripiprazole was measured 2 days after the administration, since the receptor occupancy still remains high (Kim et al. 2012) and the effect of aripiprazole might be proportionate to the brain exposure to the drug. The scans were conducted at the same time on each occasion, considering possible diurnal variation of the brain activity: the [^{11}C]raclopride scans were performed at 9:30 A.M., and the [^{18}F]FDG scans were conducted at 1:30 P.M. Blood samples for the measurement of aripiprazole plasma concentration and blood glucose level were obtained <5 min before the PET scans. The subjects performed the *N*-back task, a measure of working memory described below, within 30 min of finishing the [^{18}F]FDG scan.

PET scanning procedure and image analysis

All PET scans were performed on an ECAT EXACT 47 scanner (full-width half-maximum [FWHM]=4.6 mm) (Siemens-CTI, Knoxville, TN, USA). Before the administration of each radioligand and the acquisition of the dynamic scan, a transmission scan was performed using three Ge-68 rod sources for attenuation correction. The data from the dynamic scans were reconstructed in a 128×128×47 matrix with a pixel size of 2.1×2.1×3.4 mm by means of a filtered back-projection algorithm employing a Shepp–Logan filter, with a cut-off frequency of 0.3 cycles/pixel.

To measure brain metabolism, 370 mBq [^{18}F]FDG were injected while subjects rested in a dimly lit and quiet room for 20 min. They were instructed to remain as relaxed as possible. The PET scan began 20 min after the administration of [^{18}F]FDG.

For the data analysis, spatial preprocessing and statistical analysis were performed using the Statistical Parametric Mapping (SPM) 2 software (Institute of Neurology, University College London, UK). All reconstructed images were spatially normalized into the Montreal Neurological Institute (MNI; McGill University, Canada) standard template to remove the inter-subject anatomical variability. For the global observation of change in [^{18}F]FDG uptake, we generated mean parametric images of [^{18}F]FDG (count/pixel/s) corresponding to the dose group by averaging individual parametric values weighted using injected dose/body weight of [^{18}F]FDG. For the region-of-interest (ROI) analysis, spatially normalized images were smoothed by convolution with an isotropic Gaussian kernel, with 16 mm FWHM, to increase the signal-to-noise ratio and accommodate variations in subtle anatomical structures. Variation between

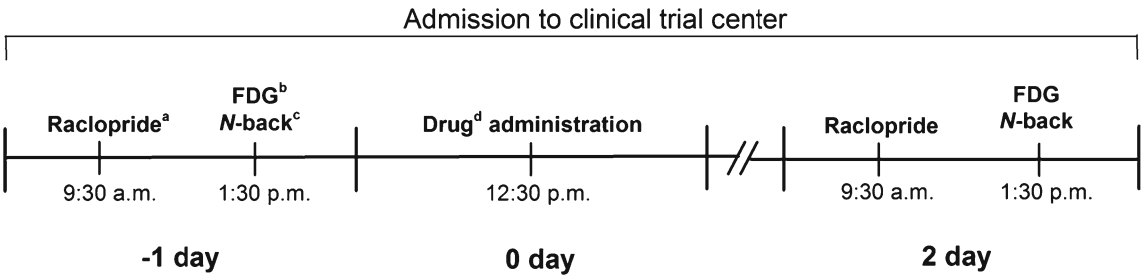

Fig. 1 Diagram for study protocol. **a** Positron emission tomography (*PET*) scanned with [^{11}C]raclopride. **b** PET scanned with [^{18}F]fluorodeoxyglucose. **c** *N*-Back task performed within 30 min after PET scans. **d** aripiprazole at 2, 5, 10 or 30 mg

scans in mean global image intensity was removed by proportional scaling, using SPM2.

We defined the frontal lobe as a primary ROI based on previous reports that antipsychotics, including aripiprazole, induce brain metabolic change in this region (Bartlett et al. 1998; Kim et al. 2008; Lane et al. 2004; Molina et al. 2003, 2005a, b) and confined the ROI analysis to the left frontal lobe because all the subjects were right-handed. Mean intensities in the left frontal lobe were quantified by averaging regional intensities, which were weighted using the probabilistic maps of the left frontal lobe (Kang et al. 2001; Lee and Lee 2005). Probability-weighted mean [^{18}F]FDG uptake for the region was calculated using the following equation, $\sum(C_i \cdot P_i)/\sum P_i$, where C_i represents for the value of ith voxel in the spatially normalized PET image, and P_i is the probability value of ith voxel in the probabilistic maps predefined in the same standard stereotaxic space.

To measure dopamine receptor occupancy by aripiprazole, dynamic 3D emission scans over 60 min (15 s× 8 frames, 30 s×16, 60 s×10, 240 s×10) were conducted after a bolus injection of 370–740 mBq [^{11}C]raclopride. Magnetic resonance (MR) images were acquired on a GE Sigma1.5-T scanner. Static PET images, obtained by combining all the frames of dynamic images, were coregistered with the MR images of the same individual. The MR images were used to define the ROI, which comprised the striatum and the reference region (the cerebellum) (Ito et al. 1998). The ROI were drawn on the subject's T1 MR image by a single rater on ten axial slices for the striatum and cerebellum. The ROIs for the striatum were drawn covering the level of Monro's foramen (Ito et al. 1998). The ROI was transferred onto the dynamic PET images to obtain the time–activity curves for the whole volume of interest (VOI) using the transformation parameters obtained by the coregistration of the static PET and MR images with SPM2. The dopamine $D_{2/3}$ receptor binding potential (BP_{ND}) in the striatum was calculated using a simplified reference tissue model (Lammertsma and Hume 1996; Olsson and Farde 2001). The dopamine D_2 receptor occupancy by aripiprazole was calculated as the percentage reduction of BP_{ND} with drug treatment, compared with the baseline:

$$\text{Occupancy}\ (\%) = \frac{BP_{ND_{baseline}} - BP_{ND_{drug}}}{BP_{ND_{baseline}}} \times 100$$

BP_{ND} parametric images of the brain were also constructed using Logan graphical approach (Logan et al. 1990) and the mean parametric images corresponding to the dose group were generated by averaging individual parametric values to observe global change in BP_{ND}.

The total dose (±SD) of radiation that each subject received in the study was 14.7±1.4 mSv.

N-back task

The *N*-back task was conducted by an independent investigator blind to the dosage of aripiprazole in order to prevent biased assessment of the task.

The stimuli were composed of numbers (1, 2, 3, 4) presented in random sequence and displayed at the points of a diamond-shaped box. In the 0-back task, which is a non-memory control condition, subjects had to press a button corresponding to the digit currently seen. The task had increasing levels of memory load as subjects were required to recollect the stimulus seen one stimulus (1-back), two stimuli (2-back) or three stimuli (3-back) beforehand while continuing to encode additional incoming stimuli. Each *N*-back task consisted of 20 stimuli and each session comprised four sets of each *N*-back task. The presentation of each *N*-back task in each session was pseudo-randomly assigned. All subjects had a preliminary session to ensure they understood the task. The subjects were instructed to respond as soon as possible. Performance data were recorded as the number of correct response and the reaction time for correct responses.

Statistical analysis

The differences in blood glucose level and brain metabolism in the left frontal lobe before and after the administration of aripiprazole were tested using a paired *t*-test.

The effects of aripiprazole and memory load on *N*-back task performance were tested using mixed effects models with the drug administration (modeled as a dummy variable: 1=before, 2=after) and *N* (memory load) as fixed effects.

Regression analysis was employed to investigate the relationship between dopamine receptor occupancy and frontal metabolic change by aripiprazole, and between frontal metabolic change and percentage change in reaction time of correct response in *N*-back task. The percentage change in reaction time is defined as follows;

$$\text{Percentage change in reation time} = \frac{\text{reaction time after medication} - \text{reaction time before medication}}{\text{reaction time before medication}} \times 100$$

To evaluate the possibility of outliers, the influence of individual data points on the regression was examined using Cook's distance test.

Results

All the subjects were scanned with [^{18}F]FDG but [^{11}C] raclopride data for one subject assigned to the 30 mg group were not acquired after aripiprazole administration due to

technical problems. Figure 2 shows the mean parametric images of [^{11}C]raclopride (BP_{ND}) and [^{18}F]FDG (count/s).

The average (±SD) plasma concentrations of aripiprazole measured just before the [^{18}F]FDG scan were 2.6±0.8 ng/ml in the 2 mg group, 5.8±1.5 ng/ml in the 5 mg group, 13.2±3.5 ng/ml in the 10 mg group and 35.4±10.8 ng/ml in the 30 mg group. The mean (±SD) dopamine receptor occupancies were 22.2±16.0 % in the 2 mg group, 35.5±3.6 % in the 5 mg group, 63.2±9.9 % in the 10 mg group and 72.8±2.1 % in the 30 mg group (Fig. 3a).

There was no significant difference in the mean (±SD) blood glucose levels measured at the same time for the two [^{18}F]FDG PET scans (87.3±6.9 mg/dl and 87.8±10.5 mg/dl, respectively; t=−0.196, df=14, p=0.848). The metabolism in the left frontal lobe was significantly decreased after the administration of aripiprazole (t=2.705, df=14, p=0.017). Figure 3b shows the frontal metabolic change according to group. The metabolic change in the frontal lobe showed a significant inverse linear relationship with striatal dopamine receptor occupancy (r=−0.659, p=0.010) (Fig. 4). There was no evidence that this relationship was driven by high-influence data points (maximal Cook's distance in this analysis was 0.401).

The mean (±SD) error rates of N-back task were 0.2±0.4 % in the 0-back task, 3.8±3.1 % in the 1-back task, 14.0±13.9 % in the 2-back task and 25.6±19.8 % in the 3-back task. There was a significant effect of memory load on the error rate but there was no effect of aripiprazole or memory load by drug interaction (N: df=3,83.8, F=29.7, p<0.001; drug: df=1,56.6, F=1.674, p=0.201; N-by-drug: df=3,85.7, F=0.783, p=0.506). The mean (±SD) reaction times for correct responses were 501.5±114.5 ms in the 0-back task, 355.7±101.5 ms in the 1-back task, 339.2±92.7 ms in the 2-back and 387.2±151.9 ms in the 3-back. The reaction time differed according to the memory load and the administration of aripiprazole (N: df=3,110.2, F=19.045, p<0.001; drug: df=1,114.3, F=5.991, p=0.016, N-by-drug: df=3,110.2, F=1.730, p=0.165). The reaction time in the 0-back task (the no memory load control condition) was not affected by the aripiprazole administration (df=1,30.0, F=0.038, p=0.846), indicating that aripiprazole did not impair reaction time per se.

There was a significant inverse linear relationship between the aripiprazole-induced change in reaction time in the highest memory load condition (3-back) and the aripiprazole-induced metabolic change in the left frontal lobe (r=−0.597, p=0.019) (Fig. 5). The maximal Cook's distance in the analysis for 3-back task was 0.511. The change of the reaction time in the 2-back task was also significantly related with the frontal metabolic change after the administration of aripiprazole (r=−0.811, p<0.001). However, after excluding one data point with a large Cook's distance index (2.86), it did not remain significant (r=−0.411, p=0.163). The change of reaction time in 0- and 1-back task did not show a significant linear relationship with the metabolic change (0-back: r=−0.169, p=0.548; 1-back: r=−0.429, p=0.126). As a post-hoc analysis, we tested the relationship between dopamine receptor occupancy and change in reaction time in 3-back task while controlling for the effect of frontal metabolic change. It did not show a significant relationship (r=−0.118, p=0.702), indicating the slower reaction time was mediated by frontal metabolic change.

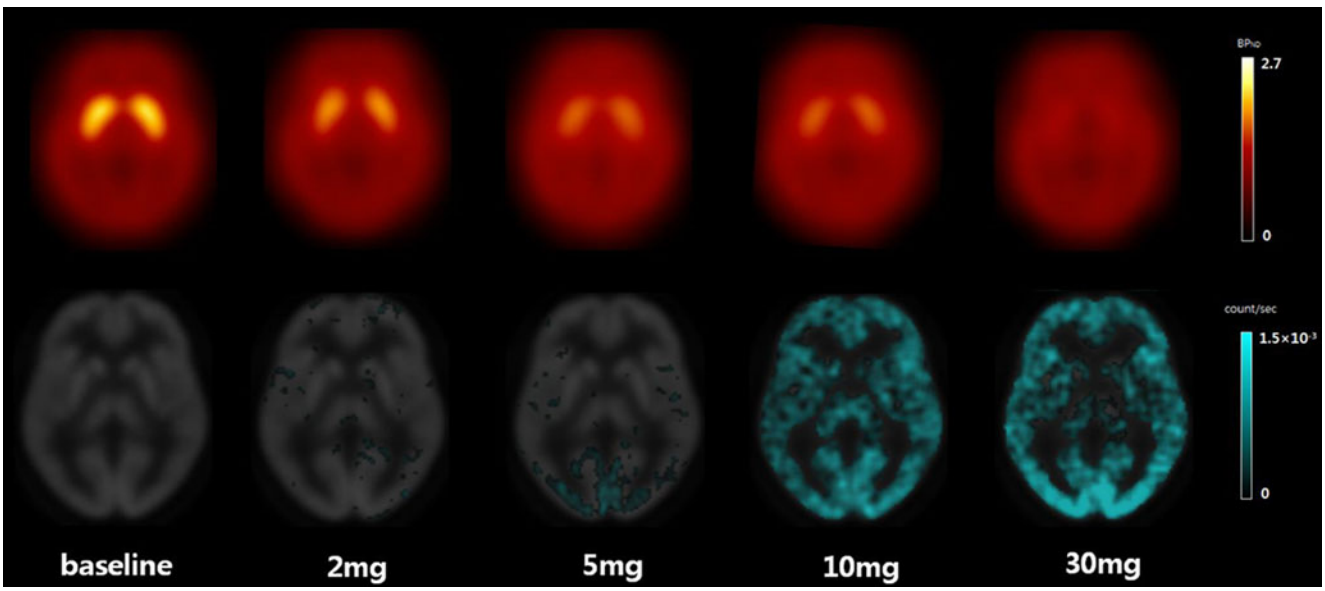

Fig. 2 Average parametric images of [^{11}C]raclopride (BP_{ND}; first row) and [^{18}F]fluorodeoxyglucose (FDG) (count/s; second row) corresponding to the dose group (each column). Each [^{18}F]FDG image had its baseline image subtracted to generate a difference image such that greater value indicates larger decrease of count after the administration of aripiprazole

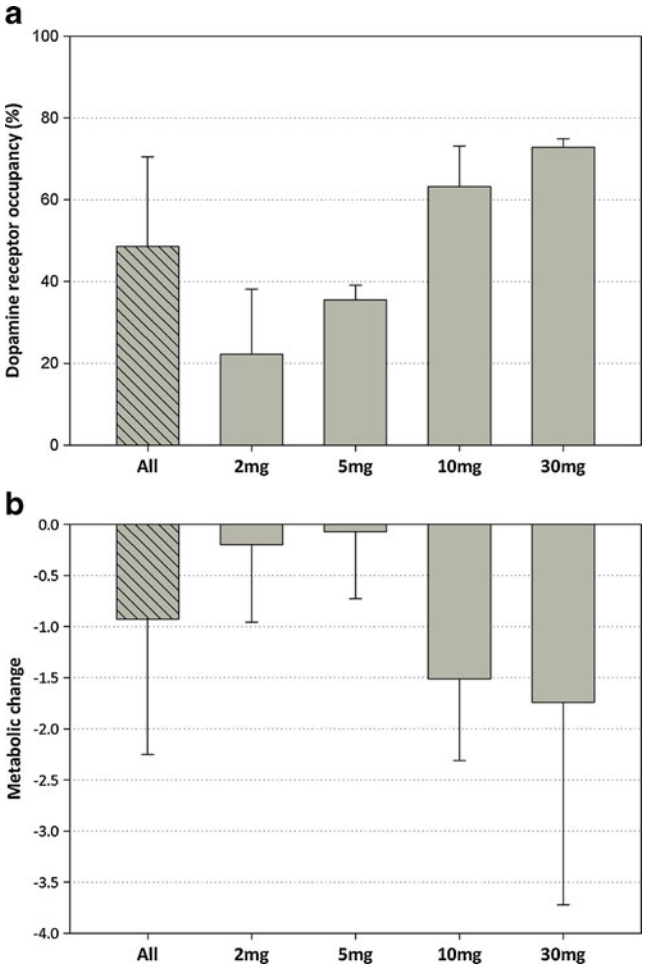

Fig. 3 Dopamine receptor occupancy (**a**) and the metabolic change in the left frontal lobe (**b**) according to the dose of aripiprazole. The error bar indicates standard deviation. Higher dopamine receptor occupancy and greater metabolic decrease were observed as the dose increased. The metabolic change was defined as the change in metabolic activity after aripiprazole administration

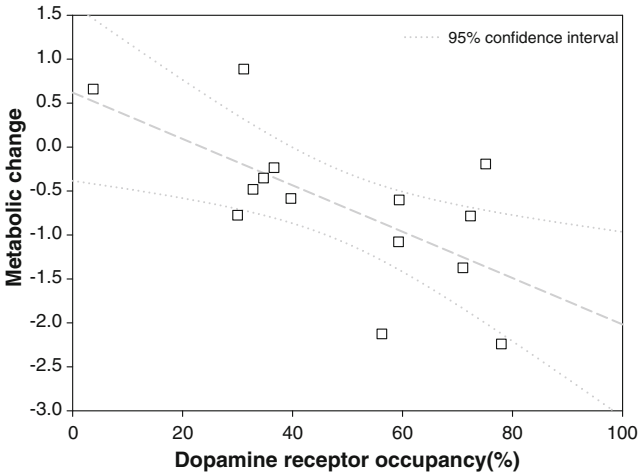

Fig. 4 The inverse linear relationship (n=14) between dopamine receptor occupancy and metabolic change in the frontal lobe after aripiprazole administration (r=−0.659, p=0.010). The metabolic change was defined as the change in metabolic activity after aripiprazole administration. [^{11}C]raclopride data for one subject assigned to the 30 mg group were not acquired after aripiprazole administration due to technical problems so that there are 14 data points in the plot

Discussion

Our main findings are that greater striatal dopamine receptor occupancy by aripiprazole was related to greater decrease in frontal lobe metabolism, and that greater reduction in frontal metabolism was associated with longer reaction times in a working memory task. These results indicate that aripiprazole may affect cognitive performance and frontal metabolism, and that the changes are linked to dopamine D_2 receptor occupancy.

In the [^{18}F]FDG PET scans, we calculated the brain metabolic change removing variation between [^{18}F]FDG scans by proportional scaling in the image processing. While this is a common approach to measuring the [^{18}F]FDG response to antipsychotic drugs (Buchsbaum et al. 2007; Lane et al. 2004; Molina et al. 2005b; Ngan et al. 2002; Potkin et al. 1994), it assumes that global brain metabolism is equal for every scan. This assumption may be violated if aripiprazole decreases absolute metabolic rate in the whole brain, as has been reported for haloperidol (Bartlett et al. 1998). The global decrease of count rate from [^{18}F]FDG parametric image could be hinting at the possibility, though the count rate is not directly reflecting absolute metabolic rate (Fig. 2). Thus we cannot exclude the possibility that our finding of decreased frontal metabolism observed in terms of relative activity in the frontal lobe reflects a global metabolic decrease.

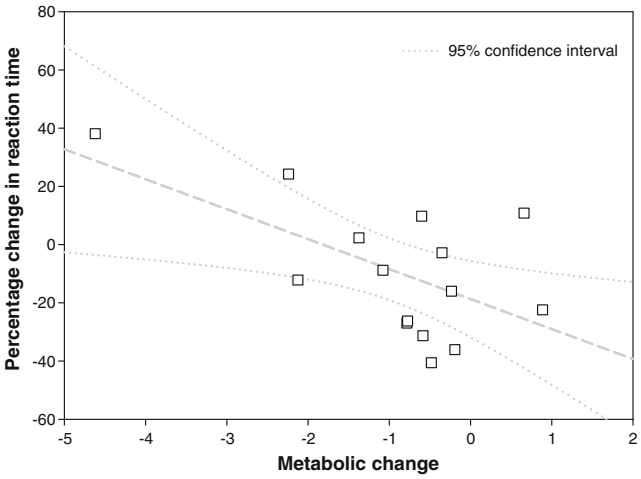

Fig. 5 The inverse linear relationship (n=15) between metabolic change in the frontal lobe and the percentage change in reaction time of correct response in 3-back task after aripiprazole administration (r=−0.597, p=0.019). The metabolic change was defined as the change in metabolic activity after aripiprazole administration

The inverse linear relationship between dopamine receptor occupancy and metabolic change suggests the brain metabolic change induced by aripiprazole is related to its effects on the dopamine system. The dopamine receptor occupancies were measured in the striatum which is rich in dopamine receptors. The striatum is linked to the prefrontal cortex via several parallel frontostriatal–midbrain loops (Calzavara et al. 2007; Eblen and Graybiel 1995; Reep et al. 2003; Simpson et al. 2010). Specifically, the striatum projects to the dopaminergic neurons in the ventral tegmental area of midbrain (Frankle et al. 2006). The striatum could thus modulate the dopaminergic inputs to the prefrontal cortex by influencing the activity of neurons in the ventral tegmental area (Simpson et al. 2010). By modulating dopaminergic activity in the striatal part of this loop, aripiprazole might alter frontal activity, and consequently decrease frontal metabolism. The clinical relevance of this is indicated by findings that altered dopaminergic function in the striatum is linked to worse performance on cognitive tasks and reduced activation in frontal cortical regions during cognitive tasks in patients with schizophrenia (Meyer-Lindenberg et al. 2002) and prodromal signs of schizophrenia (Fusar-Poli et al. 2011; Howes et al. 2009b). Abnormal prefrontal activation is directly related to pre-synaptic striatal dopamine dysfunction in people at clinical high risk for psychosis (Fusar-Poli et al. 2010).

Dopamine receptors are also found in the frontal lobe, although the density is lower than that in the striatum (Ito et al. 2008), and regional dopamine depletion in the prefrontal cortex causes cognitive dysfunction in rhesus monkeys that is reversed by a dopamine agonist (Brozoski et al. 1979). Thus it is possible that aripiprazole directly affects frontal metabolism by blocking dopamine receptors there. As striatal occupancy is likely to reflect frontal occupancy (Kegeles et al. 2008; Nyberg et al. 2002), an alternative explanation for the link between occupancy and metabolic change is that aripiprazole is having a direct effect on the frontal lobe by acting on dopamine receptors in the frontal cortex.

The decreased metabolism in the frontal lobe was related to change in performance measured by the *N*-back task, which reflects working memory (Jaeggi et al. 2010). Neuroimaging studies have consistently reported reliable activation increases in selected cortical areas with increasing memory load manipulated by the levels of *N* (see meta-analysis; Owen et al. 2005). In particular, prefrontal and parietal cortices are most commonly reported to be related to load-dependent activation change (Jaeggi et al. 2010). Our result showed that the percentage change in reaction time of correct response in the most difficult memory condition (3-back) were inversely related to the metabolic change in the left frontal lobe. In the lower memory load conditions, we did not observe a significant relationship after exclusion of an outlier (i.e., 2-back task). Although this could be a limitation of our result, this is likely due to the fact that subjects were performing almost at ceiling. The change in working memory performance was observed in reaction time measurement which shows higher reliability than response accuracies data (Jaeggi et al. 2010). Slower response could have been due to a nonspecific motor effect by D_2 blockade of aripiprazole. However, there was no effect of aripiprazole on reaction time in the 0-back task, i.e., the no-memory condition, which means slowing is related to change in cognitive performance. Taken together with the significant relationship between the receptor occupancy and the frontal metabolic change, this suggests that aripiprazole is directly impairing frontal cortical function and working memory performance. Dopamine receptor occupancy itself might have affected working memory performance. However, there was no significant relationship between dopamine receptor occupancy and change in reaction time when adjusted for the effect of frontal metabolic change. This finding suggests the frontal metabolic change following dopamine receptor occupancy by aripiprazole is mediating the effect of aripiprazole on working memory performance.

Hypofrontality is observed in drug-free patients with schizophrenia, and this is associated with the dopaminergic pathophysiology of schizophrenia and high-risk for psychosis (Fusar-Poli et al. 2010; Meyer-Lindenberg et al. 2002). Our finding that aripiprazole decreases frontal metabolism suggests that blocking D_2 receptors could further worsen hypofrontality. Taken together with findings that the primary locus of dopamine abnormality in the disorder is presynaptic (Howes et al. 2011a; and see meta-analysis, Howes et al. 2012) rather than post-synaptic, this suggests that drugs that target upstream mechanisms, rather than blocking post-synaptic D_2 receptors, may be more effective.

We investigated the relationship between dopamine receptor occupancy and brain metabolic change by aripiprazole and its influence on cognitive function in healthy volunteers. Though it has been reported that the metabolic response to antipsychotic drugs in patients with schizophrenia is similar to that in healthy volunteers (Lane et al. 2004), one must be cautious before directly extrapolating these findings to patients. One reason is that, as the dopaminergic system in patients with schizophrenia is dysfunctional (Howes et al. 2011b), it may respond differently to a partial agonist such as aripiprazole. Second, the relationship between working memory performance and dopamine receptor stimulation follows an inverted-U shape such that either too little or too much dopamine stimulation impairs working memory (Vijayraghavan et al. 2007). Since our subjects were high-functioning healthy individuals with good working memory abilities, their results may not be directly comparable with those from patients with schizophrenia who have impaired working memory, although our finding that

the effect became evident at high load suggests it may be more marked in patients who typically show poorer performance even at lower loads. As our findings were made after a single administration of aripiprazole we do not know if the same effects would be seen after long-term treatment with aripiprazole, although studies of the effects of chronic treatment with other antipsychotics suggest they would persist (Bartlett et al. 1998; Molina et al. 2003, 2005b).

Aripiprazole also has appreciable affinity for 5-HT receptors (Hirose and Kikuchi 2005). As we did not measure the effect of aripiprazole on the 5-HT system, it remains possible that effects on this system contribute to the changes we observed. It is important also to note that the correlation between frontal metabolism and striatal D_2 receptor occupancy we report does not imply causality. Furthermore, given that striatal and cortical D_2 occupancies are related (Kegeles et al. 2008; Nyberg et al. 2002), it is possible that frontal, rather than striatal, occupancy underlies the change in metabolism, although highly selective changes in striatal D_2 receptor availability have been found to lead to working memory impairments in mice, indicating that striatal occupancy could also be important (Kellendonk et al. 2006). Further work is required to disentangle these possibilities, and the potential role of other sites of action of aripiprazole, in particular the serotonin system.

Conclusions

Aripiprazole can affect cognitive function and alter frontal metabolic function, and changes in these with aripiprazole show inversely related. Metabolic change in the frontal lobe also shows a negative relationship with striatal D_2 receptor occupancy. This suggests that aripiprazole can cause secondary cognitive impairments independent of the pathophysiology of schizophrenia and that it may be important to find the lowest effective dose of aripiprazole in order to prevent adverse cognitive effects.

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