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Neural mechanisms of antidepressant efficacy of the dopamine receptor agonist pramipexole in treatment of bipolar depression

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Abstract

The D_2/D_3 receptor agonist pramipexole has clinical efficacy as an antidepressant, but its neural mechanisms are unknown. We used ^{18}FDG-PET to investigate the cerebral metabolic effects of pramipexole augmentation of mood stabilizers in bipolar II depression. Fifteen bipolar II depressed patients on mood stabilizers were imaged at baseline and following 6 wk of pramipexole (*n*=7) or placebo (*n*=8) augmentation. Relative to placebo, pramipexole treatment was associated with reductions in normalized metabolism in bilateral orbitofrontal cortex, left ventrolateral prefrontal cortex (PFC), and right anteromedial PFC. Voxel-wise analyses additionally showed decreased normalized metabolism in the left inferior parietal cortex and medial frontopolar cortical (BA 10P) area of the anteromedial PFC following pramipexole treatment. These pramipexole-induced effects on regional metabolism suggest a mechanism of antidepressant action distinct from that previously reported under serotonin reuptake inhibitor treatment and appear compatible with evidence that the central dopaminergic system plays a role in the pathophysiology of bipolar depression.

Keywords

Bipolar disorder; glucose metabolism; major depression; orbitofrontal cortex; positron emission tomography (PET)

Introduction

Pramipexole, a dopamine receptor agonist with high selectivity for the D_2 dopamine receptor family (D_2,D_3, D_4 receptor subtypes) and preferential affinity for the D_3 receptor subtype, has shown antidepressant efficacy as an augmentation strategy for treatment-resistant unipolar and bipolar depression (with effect sizes relative to placebo ranging from

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0.6 to 1.1; Aiken, 2007; Zarate *et al*. 2004). However, the neural mechanisms underlying pramipexole's antidepressant effects are unknown. In the current study, ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) imaging was used to assess the cerebral metabolic effects of pramipexole in depressed subjects with type-II bipolar disorder (BD-II). We previously demonstrated, in BD-II depression, abnormally elevated limbic-cortical-striatal activity (Mah *et al*. 2007), which has been hypothesized to partly reflect the effects of deficient mesostriatal dopaminergic input on striatal outflow (Drevets *et al*. 1992; Hasler *et al*. 2008; Mah *et al*. 2007; Swerdlow *et al*. 1987). We therefore expected that the post-synaptic D_2/D_3 receptor agonist effects of pramipexole in BD-II depression would result in reduction of normalized limbic-cortical-striatal metabolic activity (regional/global tissue radioactivity).

Methods

Participants

Fifteen subjects (12 females, mean age=43±11 yr) with BD-II in a current major depressive episode (according to DSM-IV criteria) underwent PET imaging at baseline and after 6 wk of either pramipexole (target range 1.0–3.0 mg/d; maximum dose 4.5 mg/d) or placebo administration in combination with a mood stabilizer. Subjects were a subset of the treatment-refractory BD-II sample studied in a larger clinical trial of pramipexole augmentation of mood stabilizers (Zarate *et al*. 2004). Patients were treated with lithium or divalproex sodium (VPA) for o4 wk with at least two weekly blood levels within therapeutic range (lithium, 0.6–1.2 meq./l; VPA, 50–125 mg/ml) prior to the baseline scan and subsequent randomization to pramipexole (*n*=7; three lithium, four VPA) or placebo (*n*=8; four lithium, four VPA). Patients were maintained on mood stabilizers to minimize the risk of development of hypomania or mania. No other psychotropic medications were permitted within the 2 wk (5 wk for fluoxetine) preceding the baseline scan. Subjects scored ≥20 (moderate to severe level of depression) on the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) at screening and baseline evaluations. Subjects were excluded if they had a major medical or neurological disorder, substance abuse within 3 months or dependence within 12 months, rapid cycling, psychosis, serious suicidal risk, current pregnancy, or were breastfeeding. Subjects provided written informed consent as approved by the National Institute of Mental Health Institutional Review Board.

Image acquisition and processing

PET images were acquired using a GE Advance PET scanner in 3D mode (GE Medical Systems, USA; 35 slices 4.25-mm thick; axial resolution=5.3 mm full-width half-maximum). Subjects received 4.5 mCi of ^{18}FDG following a fasting period of at least 6 h. Dynamic PET imaging of the heart in 2D mode for a total of 35 min followed, with concurrent serial venous blood sampling beginning 15-min post-tracer injection. A 10-min static emission scan was acquired 45-min post-tracer injection, followed by an 8-min transmission scan to attenuation-correct the emission scan (Carson *et al*. 1988). MRI scans were acquired to provide an anatomical framework for PET image analysis (3.0 T GE Signa Scanner; MP-RAGE sequence : TE=2.98 ms, TR=7.5 ms, inversion time= 725 ms, voxel size=0.85×0.85×1.2 mm).

The cerebral metabolic rate for glucose (CMRGlu) was quantitatively measured using a non-invasive method that combined left cardiac ventricular chamber time-activity imaging with venous blood sampling to generate the input function, a method previously validated against the more invasive approach of sampling arterial blood (Moore *et al*. 2003). This approach was well-tolerated by all subjects. However, because of the technical difficulties involved in

performing serial venous blood sampling through an intravenous cannula during PET scanning, the input function was incomplete for some subjects' pre- or post-treatment studies. Consequently, a complete set of pre- and post-treatment quantitative CMRGlu data was available for only a subset of patients. Since the sample size of this subset was insufficient to generate meaningful statistical analyses, the available quantitative CMRGlu values are provided as Supplementary material (Supplementary Table S1, available online), and only the normalized metabolic results (regional/ global tissue radioactivity) – which were available for all scan sessions – are reported here.

Clinical data analysis

The number of pramipexole responders [defined, according to convention, as individuals whose baseline MADRS score decreased ≥50% by study end (Zarate *et al*. 2004)] was compared to the number of placebo responders using a x^2 test. Between-group differences in the change in MADRS ratings pre- *vs*. post-treatment were assessed using an independent *t* test.

Region-of-interest (ROI) analysis—Each subject's PET and MRI scans were co-registered using MEDx (Medical Numerics Inc., USA). The whole-brain tissue radioactivity was measured within an MRI-based template to permit global normalization of the regional data. Regional tissue radioactivity was extracted from ROIs defined *a priori* on an MRI template image and then positioned individually on each subject's MRI scan, as described in Neumeister *et al*. (2004) (see also Supplementary material). The ROIs were defined in regions reported to have abnormal metabolism in depression (Brody *et al*. 2001; Drevets, 1999; Drevets *et al*. 1992; Mah *et al*. 2007; Mayberg *et al*. 1999): the orbitofrontal cortex (OFC), dorsolateral pre-frontal cortex (dlPFC), perigenual anterior cingulate cortex (pgACC), ventrolateral prefrontal cortex (vlPFC), anteromedial PFC (amPFC), amygdala, ventral striatum, and anterior insula (anatomical definitions for these ROI appear in Cannon *et al*. 2006; Drevets *et al*. 2002b; Neumeister *et al*. 2004; and also in the online Supplementary material). effect sizes were calculated using Cohen's *d* (Cohen, 1988) to assess the magnitude of the effects of pramipexole, relative to placebo within ROIs. effect sizes of ≥0.8 were considered large, independent of sample size. Between-group differences in metabolic change within ROIs following pramipexole or placebo treatment were assessed using independent *t* tests. Associations between clinical improvement on the MADRS, baseline metabolism, and treatment-associated metabolic changes were assessed *post-hoc* using Spearman's rho only in predefined ROIs with significant post-treatment change in metabolism. Fisher's Z transformation was used to assess differences in correlation coefficients between treatment groups (Rosenthal, 1991).

Voxel-wise analysis—Exploratory voxel-wise analyses were conducted *post-hoc* using SPM2 (Wellcome Department of Imaging Neuroscience, UK) to reduce Type-II error by identifying metabolic changes located outside the predefined ROIs and to more specifically localize the metabolic changes situated within the predefined ROIs. The co-registered PET and MRI images were spatially normalized, and smoothed using a 12-mm Gaussian kernel. Changes in metabolism following treatment were analysed in SPM2 using a randomeffects model and paired *t* tests with proportional scaling global normalization. Between-group changes were analysed using a multi-group conditions and covariates model in SPM2, with proportional scaling global normalization. The threshold for statistical significance was set at uncorrected $p<0.001$. Coordinates were converted to the stereotaxic array of Talairach & Tournoux (1988).

Results

At baseline the mean MADRS score did not differ between subjects randomized to pramipexole (34±5.8) vs. those randomized to placebo (31±5.3; t_{13}=1.1, p=0.31). Consistent with results from the larger patient sample enrolled in the clinical trial (Zarate *et al*. 2004), a greater number of BD subjects responded to pramipexole (5/7) than to placebo (1/8; χ^2=5.4, p= 0.041). The mean change on the MADRS was greater following pramipexole than placebo (pramipexole: 19.0±11.4; placebo: 6.9±7.3; t_{13}=−2.38, p=0.03).

The pre-treatment normalized metabolism did not differ between groups in any ROI. Following pramipexole treatment, normalized metabolism decreased significantly relative to placebo in the left OFC [Effect size (ES)=−1.22; t_{13}=2.37, p=0.03; Table 1] and showed non-significant trends towards decreasing in the right OFC (ES=−1.04; t_{13}=2.01, p=0.07), right amPFC (ES=−1.1; t_{13}=2.13, p=0.053), and left vlPFC (ES=−0.91, p=0.10).

Lower pretreatment normalized metabolism in the left OFC predicted superior response to pramipexole (ρ=−0.87, p=0.01; Supplementary Fig. S2). This correlation coefficient differed significantly (Fisher's Z=−2.67, p=0.008) from the corresponding association observed in the placebo group (ρ=0.43). However, the change in depression ratings was not associated significantly with the change in normalized metabolism in the same region.

The *post-hoc* voxel-wise analysis identified areas where, under pramipexole, the normalized metabolism decreased significantly in the medial frontopolar [Brodmann area (BA) 10P] cortex of the amPFC, left inferior parietal cortex, and left vlPFC, and increased significantly in the right posterior cingulate, posterior hippocampus, left motor and premotor cortices, and accumbens (Supplementary Table S2). The reductions in metabolism under pramipexole differed significantly from the metabolic changes under placebo in the left vlPFC, medial frontopolar cortex, and left inferior parietal cortex (Fig. 1). Metabolism increased in the left premotor cortex and supplementary motor area to a greater extent under pramipexole than under placebo, and increased in the left middle occipital gyrus to a greater extent under placebo than under pramipexole (Fig. 1).

We also used the voxel-wise analysis to more specifically localize the area within the OFC where metabolic activity changed most significantly under pramipexole, since our predefined ROI in this region encompassed both medial and lateral orbital gyri. Although no regional change within the OFC reached our pre-specified significance threshold of p<0.001, we observed two clusters within the OFC where changes in metabolism following pramipexole treatment reached the more liberal threshold of p<0.01. These clusters were located in the medial OFC (with the peak voxel t value situated at x=−14, y=34, z=−21; Z=2.50, p=0.006, cluster size=108 voxels) and the lateral OFC (x=38, y=36, z=−4; Z=2.41; p=0.008, cluster size=126 voxels; coordinates interpreted as in Supplementary Fig. S2).

Discussion

Clinical improvement with pramipexole augmentation in BD-II depression was associated with a reduction in normalized regional metabolism in the OFC, amPFC, and vlPFC, regions where cerebral metabolic activity is reportedly elevated in the depressed state of unipolar or bipolar mood disorders (Drevets, 1999; Drevets *et al*. 1992; Mah *et al*. 2007). *Post-hoc* voxel-wise analyses suggest that the reduction in metabolism found in the predefined ROI in the OFC was driven by reductions in both left medial orbital and right lateral orbital cortex. However, given our inability to exclude the possibility of shifts in global metabolism due to the limited sample of quantitative cerebral metabolic data, we were unable to establish whether the *absolute* CMRGlu also changed in the OFC, amPFC, and vlPFC. Nevertheless, it is noteworthy that our findings of a reduction in relative metabolism (i.e. regional/global)

in these areas following pramipexole treatment resemble the direction of metabolic changes reported in unipolar depressives following treatment with antidepressant medications or deep-brain stimulation (Drevets, 2007; Drevets *et al*. 2002a; Lozano *et al*. 2008). Further, the metabolic changes we found in depressed patients under chronic pramipexole administration appear compatible with PET data obtained in non-human primates which showed that blood flow decreased in the OFC, frontal operculum (vlPFC), insula, and cingulate cortex following *acute* pramipexole administration (Black *et al*. 2002).

In contrast to pramipexole's large effect sizes on normalized metabolic activity within the OFC, amPFC, and vlPFC, we observed small, non-significant effects in some other regions affected by selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), such as the amygdala and pgACC (Drevets *et al*. 2002a; Fu *et al*. 2004; Kennedy *et al*. 2001). However, negative findings are difficult to interpret in this small sample, e.g. the *post-hoc* voxel-wise analyses showed a cluster in the left amygdala where metabolism decreased under pramipexole treatment, but where the peak voxel *t* value corresponded to $p>0.001$ (x=−20, y=−1, z=−17; Z=1.88, $p= 0.03$, $k=4$), raising the possibility of Type II error.

The association between lower pretreatment metabolism in the OFC and superior response to pramipexole is noteworthy in light of previous reports of inverse relationships between OFC activity and depression severity in major depressive disorder (Drevets, 2007; Drevets *et al*. 1992) and BD (Mah *et al*. 2007), reduced OFC activity in treatment-resistant depression (Mayberg *et al*. 2000), and elevated risk for development of depression with reduced OFC volume (Lai *et al*. 2000). These data, taken together with pre-clinical evidence of modulatory effects of OFC over emotional expression, are consistent with hypotheses that increased OFC activity reflects a compensatory response in depression (Drevets, 2007). The inverse relationship between OFC metabolism and response to pramipexole suggests that those least capable of mounting this compensatory response are most likely to benefit from pramipexole.

A limitation to interpreting the specificity of our findings was that the sample size was too small to establish whether pramipexole treatment significantly altered global CMRGlu, particularly since technical problems precluded analysis of quantitative CMRGlu for some subjects (see Methods section). Black *et al*. (2002) reported significant dose-related decreases in whole-brain cerebral blood flow (CBF) following *acute* pramipexole administration in healthy baboons ($n=7$, $p<0.05$), with a maximal change of −23 % at the intermediate dose tested of 50 μg/kg i.v. It is unclear whether such an effect would be expected under the experimental conditions of our study, in which pramipexole was administered *orally* on a *chronic* basis to human subjects with BD. Moreover, while CMRGlu and CBF are coupled under resting conditions, dopamine agonists may exert non-specific vascular effects that could alter CBF without affecting CMRGlu. Nevertheless, if chronic pramipexole administration similarly reduced global CMRGlu, then the reductions in normalized metabolism we observed in the OFC, amPFC and vlPFC under pramipexole would remain interpretable, since they would become more pronounced without global normalization. In contrast, under this scenario the findings of *increased* normalized metabolism in motor and premotor cortices, supplementary motor area, and accumbens area (Supplementary Table S2) would be considered non-specific since they may have been driven by a reduction in CMRGlu in other regions.

In summary, the present study suggests that the antidepressant efficacy of pramipexole augmentation for bipolar depression may have neural mechanisms that are partly similar to, and partly distinct from, those associated with other somatic antidepressant therapies.

Further, the pramipexole-induced effects on regional metabolism provide additional support for a role of the central dopaminergic system in the pathophysiology of bipolar depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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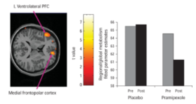

Regional effect	Number of voxels in cluster	x, y, z[a] coordinates	Z value[b]	Cluster-level corrected p
Metabolism decreased during pramipexole, unchanged during placebo				
L ventrolateral PFC (BA 46)	812	−43, 26, 18 −45, 29, 9	3.43 3.29	0.15
L inferior parietal lobule (BA 40)	1772	−55, −38, 36	4.68[c]	0.004
L lateral cerebellum (BA 37)	549	−42, −56, −20	2.98	0.42
Metabolism increased during pramipexole, unchanged during placebo				
L premotor cortex (BA 6)	1378	−18, −13, 47 −5, −18, 58	3.87[c] 3.57[c]	0.017
Supplementary motor area[e] (BA 6)	1378	−1, −9, 47	3.73[c]	0.017
Metabolism decreased during pramipexole to greater extent than during placebo[d]				
Medial frontopolar cortex (BA 10P)	343	9, 50, 13 −4, 63, 5	3.46 3.06	0.81
Metabolism unchanged during pramipexole, increased during placebo				
L middle occipital gyrus (BA 39)	1772	−46, −79, 26	3.08[c]	0.004

[a] Stereotaxic coordinates locate peak voxel t values corresponding to p<0.001 that also are part of clusters of significant voxels that are significant at p<0.05 by the cluster test (Poline et al. 1997). Coordinates denote the distance in mm from the anterior commissure, with positive x and y indicating right and anterior, respectively, and positive z dorsal to a plane containing both the anterior and posterior commissures.

[b] The voxel level Z value for the voxel containing the peak difference.

[c] Significant at p<0.05 after applying corrections for multiple comparisons using the cluster-test (Poline et al. 1997).

[d] The metabolic reduction under placebo was significant at p (uncorrected) <0.05 but was not significant at p<0.05 after correction for multiple comparisons using the cluster test (Poline et al. 1997). The t value shown in table above indicates that the reduction in this region under pramipexole was significantly greater than the reduction under placebo.

[e] Anatomical nomenclature after Petit et al. (1998).

Fig. 1.

Regions of interest identified by voxel-wise analysis where changes in normalized metabolism associated with pramipexole treatment differed from those associated with placebo administration, as shown by (*top left*) horizontal section from the statistical parametric map of voxel t values computed using SPM2, $p<0.001$; (*top right*) fitted parameter estimates for regional/global metabolism (in which the mean value for individual subject is set to 50) in left ventrolateral prefrontal cortex; (*bottom*) table of stereotaxic coordinates of regions where changes in normalized metabolism associated with pramipexole treatment differed from those associated with placebo administration. PFC, Prefrontal cortex; L, left.

Table 1

Changes in normalized cerebral glucose metabolism (mean, standard deviation) in subjects randomized to receive either pramipexole or placebo and effect sizes of pramipexole in regions-of-interest defined *a priori*

Region of interest	Effect size (Pram/placebo)	Pramipexole		Placebo	
		Pre	Post	Pre	Post
Orbitofrontal cortex					
Left[a]	−1.22	1.14 (0.036)	1.10 (0.058)[c]	1.15 (0.031)	1.15 (0.039)
Right[b]	−1.04	1.12 (0.042)	1.08 (0.049)[c]	1.13 (0.037)	1.12 (0.033)
Ventrolateral PFC					
Left[b]	−0.91	1.14 (0.035)	1.11 (0.042)[d]	1.18 (0.040)	1.19 (0.060)
Right	−0.39	1.13 (0.033)	1.10(0.034)	1.17 (0.053)	1.16 (0.059)
Anteromedial PFC					
Left	−0.59	1.04 (0.035)	1.01 (0.049)	1.08 (0.077)	1.09 (0.068)
Right[b]	−1.10	1.09 (0.043)	1.04 (0.046)[c]	1.09 (0.072)	1.09 (0.080)
Perigenual ACC					
Left	0.78	1.11 (0.053)	1.12 (0.062)	1.15 (0.065)	1.12 (0.051)[d]
Right	−0.07	1.10 (0.075)	1.09 (0.058)	1.10 (0.068)	1.10 (0.068)
Dorsolateral PFC					
Left	−0.48	1.20 (0.036)	1.18 (0.043)	1.22 (0.047)	1.21 (0.063)
Right	−0.28	1.19 (0.064)	1.18 (0.053)	1.20 (0.058)	1.21 (0.060)
Amygdala					
Left	0.27	0.94 (0.097)	0.94 (0.075)	0.86 (0.111)	0.84 (0.107)
Right	0.14	0.92 (0.062)	0.93 (0.055)	0.86 (0.063)	0.86 (0.060)
Ventral striatum					
Left	−0.01	1.25 (0.100)	1.27 (0.086)	1.24 (0.099)	1.26 (0.052)
Right	0.37	1.31 (0.100)	1.31 (0.139)	1.26 (0.067)	1.24 (0.087)
Anterior insula					
Left	−0.62	1.22 (0.051)	1.18 (0.066)	1.24 (0.058)	1.24 (0.093)
Right	0.49	1.20 (0.070)	1.20 (0.062)	1.25 (0.070)	1.21 (0.110)

ACC, Anterior cingulate cortex; PFC, prefrontal cortex.

Effect sizes (ES) of pramipexole relative to placebo in regions-of-interest calculated as the difference between mean pramipexole- and placebo-mediated metabolic change divided by the pooled standard deviation for the two means (Cohen, 1988).

ES: 0.2 = small, 0.5 = medium, 0.8 = large. A larger ES indicates greater percentage of non-overlap in the distribution of scores for the active treatment group with placebo group; e.g. an ES of 1.0 indicates a non-overlap of 55.4% of the two distributions.

[a] Metabolic change during treatment differed between groups ($p<0.05$).

[b] Metabolic change during treatment showed non-significant trend towards differing between groups at $0.05<p\leq0.10$.

[c] Post-treatment metabolism changed from baseline at $p<0.05$.

[d] Post-treatment metabolism showed non-significant trend towards differing from baseline at $0.05<p<0.10$.

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