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cAMP Signaling in Brain is Decreased in Unmedicated Depressed Patients and Increased by Treatment with a Selective Serotonin Reuptake Inhibitor

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Abstract

Basic studies exploring the importance of the cyclic adenosine monophosphate (cAMP) cascade in major depressive disorder (MDD) have noted that the cAMP cascade is downregulated in MDD and upregulated by antidepressant treatment. We investigated cAMP cascade activity by using ^{11}C-(*R*)-rolipram to image phosphodiesterase-4 (PDE4) in unmedicated MDD patients and after approximately eight weeks of treatment with a selective serotonin reuptake inhibitor (SSRI). ^{11}C-(*R*)-rolipram PET scans were performed in 44 unmedicated patients during a major depressive episode and 35 healthy controls. Twenty-three of the 44 patients had a follow-up ^{11}C-(*R*)-rolipram PET scan approximately eight weeks after treatment with an SSRI. Patients were moderately depressed (Montgomery-Åsberg Depression Rating Scale=30±6) and about half were treatment-naïve. ^{11}C-(*R*)-Rolipram binding was measured using arterial sampling to correct for individual differences in radioligand metabolism. We found in unmedicated MDD patients widespread, ~20% reductions in ^{11}C-(*R*)-rolipram binding compared to controls (P=0.001). SSRI treatment significantly increased rolipram binding (12%, P<0.001) with significantly greater increases observed in older patients (P<0.001). Rolipram binding did not correlate with severity of baseline symptoms, and increased rolipram binding during treatment did not correlate with symptom improvement. In brief, consistent with the results of basic studies, PDE4 was decreased in unmedicated MDD patients and increased after SSRI treatment. The lack of correlation between

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Conflict of Interest

Dr. Zarate is listed as a co-inventor on a patent for the use of ketamine and its metabolites in major depression. Dr. Zarate has assigned his rights in the patent to the US government but will share a percentage of any royalties that may be received by the government. All other authors have no conflict of interest to disclose.

PDE4 binding and depressive symptoms could reflect the heterogeneity of the disease and/or the heterogeneity of the target, given that PDE4 has four subtypes. These results suggest that PDE4 inhibitors, which increase cAMP cascade activity, may have antidepressant effects.

Keywords

cAMP; second messenger; selective serotonin reuptake inhibitor; positron emission tomography; major depressive disorder

Introduction

The key role of the cyclic adenosine monophosphate (cAMP) cascade in depression is thought to involve both pathological changes in unmedicated patients as well as a common pathway for various antidepressants to produce antidepressant effects. Human postmortem studies in individuals with depressive disorders have indicated low cAMP signaling [1–3]. Correspondingly, multiple rodent studies and one human postmortem study showed that various forms of chronic, but not acute, administration of antidepressants upregulate cAMP signaling [2, 4]. Based on these findings, the cAMP theory of depression posits low cAMP signaling in unmedicated patients and, commensurately, upregulation of cAMP signaling as a mechanism of antidepressant treatment. Here, we sought to examine these two theories in patients with major depressive disorder (MDD) using the positron emission tomographic (PET) radioligand ^{11}C-(*R*)-rolipram, a reversible inhibitor of phosphodiesterase-4 (PDE4).

PDE4 is the primary enzyme in brain to metabolize cAMP to the inactive monophosphate, thereby terminating cAMP signaling. Because of a feedback mechanism, rolipram binding to PDE4 provides a measure of the activity of this enzyme. Essentially, increased cAMP stimulates protein kinase A (PKA), which phosphorylates PDE4 [5]. This, in turn, increases both enzymatic activity of PDE4 and rolipram binding affinity [6]. Previous work from our laboratory confirmed biochemical studies of this phosphorylation effect using in vivo PET imaging in rats; as predicted, local injection into brain of a PKA activator increased in vivo binding of ^{11}C-(*R*)-rolipram to PDE4, and injection of a PKA inhibitor had the opposite effect [7].

Because anoxia leads to dephosphorylation of PDE4 within minutes, postmortem measurements of PDE4 enzymatic activity and rolipram binding require rapid removal of brain, which is possible in animals but not in humans. For this reason, we used in vivo binding of ^{11}C-(*R*)-rolipram to assess cAMP signaling in humans. A previous study from our laboratory found that, consistent with the cAMP theory of depression, ^{11}C-(*R*)-rolipram was decreased by about 20% in all areas of the brain in unmedicated MDD patients currently experiencing a major depressive episode [8]. Building on this work, the main purpose of the present study was to test the cAMP theory of the mechanism of antidepressant response. More specifically, we hypothesized that two months of treatment with an SSRI would increase ^{11}C-(*R*)-rolipram binding in the brain of MDD patients experiencing a major depressive episode and that this increased binding would correlate with symptom improvement. We also compared rolipram binding between healthy controls and

unmedicated MDD patients in a larger sample than in our previous study [8] to confirm downregulation of cAMP signaling in unmedicated patients.

Materials and Methods

Participants

This study was approved by the Institutional Review Board of the National Institute of Mental Health and the Radiation Safety Committee of the National Institutes of Health. Informed consent was obtained from all subjects. For the baseline PET scan, participants included all those in our prior study [8] plus 10 additional control subjects and 16 additional MDD patients. This brought the total number of participants to 35 controls and 44 MDD patients, which is more than twice the number enrolled in most PET molecular imaging studies in brain (Table 1). Because all of these participants were recruited continuously in the same manner, we report results for all subjects together. The patients met DSM-IV criteria for MDD [9] and were currently experiencing a major depressive episode without psychotic features (n=44). All patients were unmedicated at the time of the first ^{11}C-(*R*)-rolipram PET scan; about half were treatment-naïve and the other half had been free from psychotropic medications for an average of 28 months. Patients were required to have a score of ≥20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) [10] at the time of the first PET scan. Patients were moderately depressed at that time as assessed by the MADRS (30±6).

Twenty-three of the 44 unmedicated MDD patients had a second ^{11}C-(*R*)-rolipram PET scan 7.9±1.7 weeks after starting an SSRI (citalopram for 19 patients, escitalopram for one, and sertraline for three; all patients received only monotherapy). As long as SSRI treatment was clinically appropriate, all patients were asked if they were willing to have SSRI treatment and then have another PET scan. SSRIs were given under this research protocol. No patient was removed from the study after starting an SSRI because of symptom worsening or because no therapeutic effect was observed. Clinical characteristics between those who had only a baseline ^{11}C-(*R*)-rolipram scan and those who had two PET scans were mostly similar except for gender balance; only one female patient agreed to have two PET scans.

Healthy controls had no history of a major psychiatric or neurological disorder and no first-degree relative with a mood or psychotic disorder. Controls and patients were well matched in terms of sex, age, and cigarette smoking (P>0.80). To study the reproducibility of the PET measurement, 13 of 35 healthy controls had a second PET scan without medication at an interval of 8.0±2.1 weeks.

All patients and controls were between 18 and 55 years of age and in good physical health. See Supplementary Information for more details.

Data acquisition

Evaluation of Symptom Severity—Severity of depressive and anxiety symptoms was assessed for both control subjects and MDD patients using the MADRS, the 17-item Hamilton Rating Scale for Depression (HDRS-17) [11], and the Hamilton Rating Scale for Anxiety (HAM-A) [12].

Brain Imaging—PET, magnetic resonance imaging (MRI), and data processing were conducted as previously described [8]. After intravenous administration of ^{11}C-(*R*)-rolipram, PET images were acquired for 90 minutes. To calculate ^{11}C-(*R*)-rolipram binding in the brain—which is not influenced by cerebral blood flow or peripheral clearance—unmetabolized ^{11}C-(*R*)-rolipram levels in arterial plasma were measured for 90 minutes. Because only free ^{11}C-(*R*)-rolipram enters the brain, plasma free fraction (f_P) of ^{11}C-(*R*)-rolipram was measured using arterial plasma in each scan. High-resolution anatomical MRI scans were performed for every subject except two MDD patients who had only clinical MRI scans. High-resolution MRI scans were used to analyze PET data after transforming into the single standard space (Montreal Neurological Institute space). Data from the two patients without high-resolution MRI scans were analyzed in a similar way by using a template image of ^{11}C-(*R*)-rolipram as described previously [8].

Calculation of ^{11}C-(*R*)-Rolipram Binding in Brain—^{11}C-(*R*)-Rolipram binding levels were measured by compartmental modeling as total distribution volume (V_T/f_P) [13] in 10 large preselected regions covering most brain areas: frontal, parietal, lateral temporal, occipital, medial temporal, and anterior cingulate cortices; caudate; putamen; thalamus; and cerebellum. Right- and left-side data were combined for each region. Two additional analyses were performed. First, to investigate possible changes in rolipram binding in small regions, V_T/f_P was calculated in each volume element (i.e., voxel) of the images by Logan plot [14], and parametric images were created where each voxel value was V_T/f_P. These parametric images were analyzed using Statistical Parametric Mapping (SPM) version 2008 (SPM8; Wellcome Trust Centre for Neuroimaging, London, United Kingdom). Second, to eliminate the influence of individual differences in gray matter volume, partial volume correction [15] was applied to the parametric images using MRI images segmented to gray and white matter. Rolipram binding levels in the 10 regions were subsequently measured.

Statistical Analysis—Group comparisons and correlation/regression analyses were performed for both regional and voxel data. Correlation/regression analyses were performed by controlling for possible confounding factors such as age and gender. See Supplementary Information for details. Results are shown as mean ± SD.

Results

Baseline scans without medications: The larger sample size in the current study confirmed the previous finding of decreased ^{11}C-(R)-rolipram binding in unmedicated MDD patients

The current study expanded our previous work to include a larger sample size of 35 healthy controls and 44 unmedicated patients [8]. Our results confirmed our previous finding of widespread significant decreases in ^{11}C-(*R*)-rolipram binding. The decrease was highly significant, with an average change of −18% (Fig. 1, P=0.001, F=11.45, df=1,77 for group difference in the 10 regions analyzed using repeated measures, two-way analysis of variance with regions as the within subjects factor, Cohen's d=0.77). The magnitude of the decrease was similar across the 10 large preselected regions across brain (range= −17% to −21%). The analysis using each voxel data and SPM confirmed widespread and similar magnitudes

of decrease across brain areas found by the analysis based on large regions. SPM analysis with no global normalization detected highly significant decreases in most brain areas with family-wise-error (FWE)-corrected P<0.001. After applying global normalization, i.e., adjusting the average between controls and unmedicated patients, no small region in unmedicated patients showed a significantly greater or smaller decrease than other brain regions.

Other findings in this larger sample of controls vs. unmedicated patients were similar to those reported previously. The decrease in rolipram binding was not caused by the potentially smaller volume of brain regions in patients reported in the literature [17] because PET data corrected for volume of gray matter (i.e., partial volume correction) showed highly significant decreases in rolipram binding in unmedicated patients (−15%, P=0.005, F=8.31, df=1,75, Cohen's d=0.67; two patients who did not have high resolution structural MRI were not included). Patients who smoked cigarettes (n=10) had significantly lower rolipram binding (−23%) than non-smoking patients (n=34) (P=0.027, F=5.25, df=1,42, Cohen's d=0.71), although healthy controls showed no difference (3%) between smokers and non-smokers. After removing eight smokers from the control group and 10 smokers from the unmedicated patients group, 34 non-smoker unmedicated patients showed 14% lower rolipram binding than 27 non-smoker controls (P=0.025, F=5.309, df=1,59, Cohen's d=0.60). Neither history of prior antidepressant treatment, comorbid anxiety disorders, nor gender affected rolipram binding in unmedicated patients (P>0.21).

Age and gender were possible confounding factors that affected baseline rolipram binding

The current larger sample allowed us to investigate possible confounding factors that might have affected rolipram binding. The previous smaller sample [8] did now allow us to perform such investigations. In particular, age and gender affected rolipram binding, and these confounding factors might have made it difficult to detect a possible relationship between severity of symptoms and rolipram binding. Specifically, our analyses showed that, when controlling for age, no correlation between baseline rolipram binding and severity of symptoms was observed. In addition, interactions between rolipram binding, symptom severity, and age were found in male, but not female, patients.

Significant correlations between baseline rolipram binding and MADRS scores were observed in 32 male patients in nine of 10 large regions (P=0.008–0.029). However, in all regions for male patients, rolipram binding was significantly negatively correlated with age (P<0.039 in all regions). Furthermore, older male patients tended to show more severe symptoms as measured by the MADRS (P=0.061). When controlling for age, the partial correlation between baseline rolipram binding and MADRS score was significant only in the frontal cortex (P=0.039 without correction for multiple comparisons) but not in other areas. An SPM regression analysis that controlled for age in male patients detected no significant relationship between severity of symptoms and rolipram binding. Taken together, these analyses suggest that age was a key factor in the correlation between rolipram binding and MADRS score, but that there was inadequate evidence of a relationship between rolipram binding and MADRS score. Notably, female patients showed no correlation between baseline rolipram binding and severity of symptoms or age (P>0.14). In addition, healthy

subjects showed almost no correlation between rolipram binding and age, regardless of gender. Male healthy controls showed a significant negative correlation only in the cerebellum (P=0.031) but not in any other region (P=0.053–0.44).

SSRI treatment increased ^{11}C-(R)-rolipram binding

Two months of SSRI treatment significantly increased rolipram binding in the 23 MDD patients. The increase was highly significant (P<0.001, F=17.34, df=1,21 using age as a covariate). The average increase across brain regions was 12% (10% in 18 non-smokers and 15% in five cigarette smokers, Cohen's d for all patients=1.82), with marked intersubject variability of SD 36%. The magnitude of the increase was similar across regions, ranging between 10%–12%. Echoing the findings for the baseline scans in 32 unmedicated male patients described in the previous subsection, these 23 patients, predominantly male, similarly showed significant negative correlations between baseline rolipram binding and age (Fig. 1A, P=0.001–0.024 across 10 large regions by both Pearson and Spearman correlation). After SSRI treatment, the correlation between rolipram binding and age disappeared (Fig. 1B, P>0.39 in all regions by both Pearson and Spearman correlation). This is because older patients showed significantly greater SSRI-induced increases in rolipram binding (Suppl. Fig. 1). The association between age and increase in rolipram binding was highly significant in all 10 regions (r=0.69–0.72, P<0.001).

SSRI-induced increases in rolipram binding did not correlate with symptom improvement

Of the 23 patients receiving SSRI treatment, 10 had a greater than 50% decrease in MADRS score, and three patients remitted (MADRS<10). Overall, SSRI treatment decreased MADRS score from 30±6 to 18±11, HDRS-17 from 20±5 to 14±8, and HAM-A from 19±5 to 12±8 (P<0.001 for all three scales, t=4.7–6.0).

Although SSRI treatment significantly increased rolipram binding, there was no correlation between increased rolipram binding and improvement of depressive or anxiety symptoms as assessed by the MADRS, HDRS-17, or HAM-A, regardless of whether the correlation was controlled for age or not (P>0.11).

PET measurement of ^{11}C-(R)-rolipram binding showed good reproducibility

In contrast to the increased rolipram binding observed after SSRI treatment in the 23 MDD patients, 13 healthy controls who had two rolipram PET scans at similar time intervals but without SSRI treatment showed no change in rolipram binding (−1±13%, P=0.25, F=1.48, df=1,11).

Discussion

This study is the first to provide evidence for the cAMP theory of depression in living, unmedicated MDD patients and in response to SSRI treatment. The 44 unmedicated MDD patients in this study demonstrated significantly decreased activity in the cAMP cascade, as indicated by 18% lower ^{11}C-(*R*)-rolipram binding compared to control subjects. Two months of SSRI treatment significantly increased cAMP activity, as indicated by the 12±36% increase in rolipram binding compared to the patient's own baseline scans. No correlation

was observed between rolipram binding and symptom severity, neither for the unmedicated baseline scan nor in response to SSRI treatment, possibly due to the heterogeneity of the disorder or the heterogeneity of PDE4, which has four distinct subtypes.

Both decreased rolipram binding in unmedicated patients at baseline and normalization by SSRI are largely in line with previous findings from postmortem studies in patients with MDD and suicide victims as well as those from rodent studies where antidepressants were administered to normal animals. The postmortem studies suggested an overall decrease in cAMP cascade activity in unmedicated patients because several components of signal transduction decreased, not only PDE4 [2, 3, 18–20]. The rodent studies reported that various antidepressant treatments increased multiple components of the cAMP cascade [4]. A previous rodent study from our laboratory indicated that ^{11}C-(*R*)-rolipram PET imaging detected cAMP cascade activity—both increased activity induced by a PKA activator, and decreased activity induced by a PKA inhibitor [7]. Because PDE4 activity is regulated by its phosphorylation status and because the phosphorylated form of PDE4 is more sensitive to enzyme inhibition by rolipram [6], our rodent study indicated that ^{11}C-(*R*)-rolipram PET reflects the enzymatic activity of PDE4, not only the amount of enzyme. Taken together these postmortem, rodent with antidepressant administration, and our rodent PET studies, the present findings provide strong evidence for the cAMP theory of depression, specifically that the cAMP cascade is downregulated in unmedicated MDD patients and increased—perhaps even normalized—by SSRI treatment.

The heterogeneity of depression

MDD has long been thought to be a heterogeneous disorder, and our own study shows such heterogeneity in the effects of sex and age on the PET results. The larger sample size in the present study allowed us to expand our investigation into the relationship between baseline rolipram binding, symptom severity, age, and gender. In unmedicated patients, significant age-related decreases in rolipram binding were observed in male, but not female, MDD patients; no such association was noted in male or female healthy controls, which may indicate that the activity of the cAMP cascade does not normally decrease until the mid-50s. The fact that age-related decreases were found only in male MDD patients suggests that these decreases may be related to the pathophysiology of MDD. Interestingly, postmortem studies reported mixed results regarding age-related changes in the cAMP cascade in MDD patients and suicide victims. One study found age-related decreases in ^{3}H-cAMP binding in the parietal cortex [21] while others found no age-related changes in cAMP binding [18] or cAMP regulatory element protein [2]. It should be noted, however, that these postmortem studies may not reflect in vivo activity of the cAMP cascade because the phosphorylation and activity of the key enzyme PDE4 change after death, as indicated by the different affinity of (*R*)-rolipram binding between in vitro and in vivo measurements [22]. Moreover, these postmortem studies were limited by their small sample sizes (n=10–17), differences in postmortem intervals, and medication history of the subjects. Dysregulation of the cAMP cascade has been linked to cognitive decline in both normal elderly people and patients with Alzheimer's disease [23]. Furthermore, a PDE4 subtype D selective inhibitor was shown to improve cognitive function in a mouse model of Alzheimer's disease [24].

In the present study, and in contrast to male patients, female patients showed no correlation between rolipram binding and age or severity of symptoms. To our knowledge, no report of the effects of gonadal hormones on PDE4 exists; nevertheless, it is possible that gonadal hormones may affect PDE4 in humans. Should that be the case, PET scans at various stages of the menstrual cycle might have confounded the results. No female patients were taking oral contraceptive medications. The present findings suggest that the possible confounding factors of age and gender may need to be taken into account in any future therapeutic trials of subtype selective PDE4 inhibitors. Because only one female patient had a second PET scan, changes in PDE4 after SSRI remain unknown in females.

Heterogeneity of PDE4

PDE4 is known to have four subtypes—A, B, C, and D. Among these, subtypes B and D have been studied extensively mice. One of regulators for PDE4B enzyme activity is the scaffold protein, *Disrupted in schizophrenia 1 (DISC1)*, which mediates multiple intracellular signal transduction pathways [25] and is associated with a number of psychiatric disorders, including schizophrenia, mood disorders, and autism [26]. PDE4B is also thought to be linked to anxiety symptoms, as PDE4B knockout mice show anxiogenic behaviors [27]. In MDD patients, increased PDE4B mRNA was found in leucocytes; levels decreased after antidepressant treatment [28]. Studies of PDE4D knockout mice indicated that this subtype is involved in depressive symptoms; specifically, PDE4D knockout mice showed reduced immobility time in the forced swim and tail suspension tests [29]. PDE4D knockout mice also displayed cognitive enhancement, suggesting that PDE4D may be involved in cognitive functioning [30].

Inhibition of PDE4 as Antidepressant Therapy

Rolipram, which non-selectively inhibits all four PDE4 subtypes, was previously evaluated as an antidepressant. Open-label trials in approximately 200 depressed patients (mostly with endogenous or chronic depression, often treatment-resistant) suggested that rolipram had antidepressant properties [31]. In addition, some patients treated with rolipram showed rapid antidepressant effects within two to four days [31, 32]. However, subsequent controlled studies found rolipram to have a similar onset of action and either comparable [33, 34] or lower [35] efficacy than tricyclic antidepressants [33, 34]. It should be noted that most of these trials had small sample sizes and that dose titration was restricted due to nausea and vomiting. As a result, rolipram was not further developed as an antidepressant.

Subsequent to the therapeutic trials of rolipram in depression, PDE4 was discovered to have four distinct subtypes, which suggests that a subtype selective inhibitor might have antidepressant efficacy without side effects. In fact, animal studies suggest that PDE4D is responsible for nausea [36]. However, those studies do not exclude the possibility that simultaneous inhibition of multiple subtypes (e.g., PDE4B and PDE4D) may act synergistically, so that a single subtype inhibitor would cause relatively little nausea. Thus, an inhibitor of only PDE4B or PDE4D, the two predominant subtypes in brain, might have antidepressant efficacy but lack side effects.

Taken together with previous findings, the present results support the cAMP theory of depression. We found that the cAMP cascade was downregulated in unmedicated MDD patients currently experiencing a major depressive episode, and upregulated by two months of SSRI treatment. While the lack of correlation between increased rolipram binding and improvement in symptoms raises significant questions about the role of cAMP signaling in MDD, this finding could be due to the heterogeneity of the disorder, the existence of distinct PDE4 subtypes, or interactions between age, gender, and the cAMP cascade. It should be noted that initial clinical trials of rolipram [31–35] did not perform post-hoc analyses using age or gender. In our opinion, the overall strength of prior and current PET studies supports investigating the role of PDE4 subtypes in the pathophysiology of MDD as well as the possibility that subtype selective inhibitors can be an effective treatment for depression. Our results further suggest that age and gender should be taken into account to properly evaluate the effect of new PDE4 inhibitors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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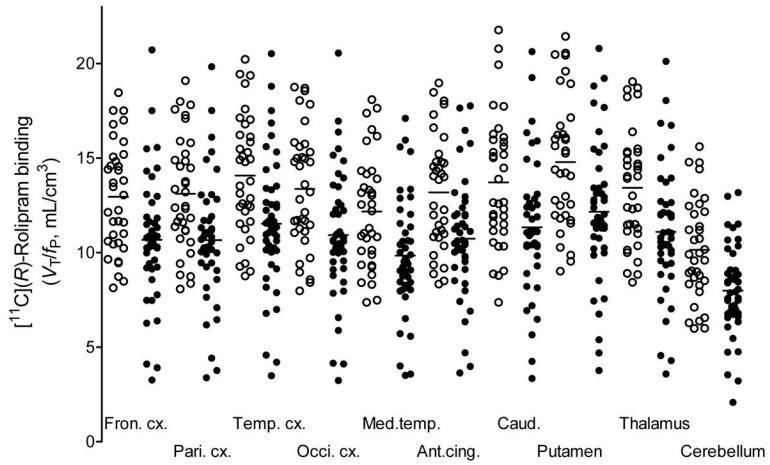

Figure 1.

^{11}C-(*R*)-Rolipram binding levels in healthy controls (open symbols) and unmedicated patients with major depressive disorder (MDD, closed symbols) measured as total distribution volume, V_T/f_P, by unconstrained two-compartment model using brain data in large regions. MDD patients showed a widespread and almost uniform decrease of 17%–21% across 10 brain regions (P=0.001). Mean (95% confidence interval) values across the 10 regions were 13.1 (12.0 – 14.1) and 10.7 (9.8 – 11.6) for healthy controls and unmedicated patients, respectively. Bars indicate group means.

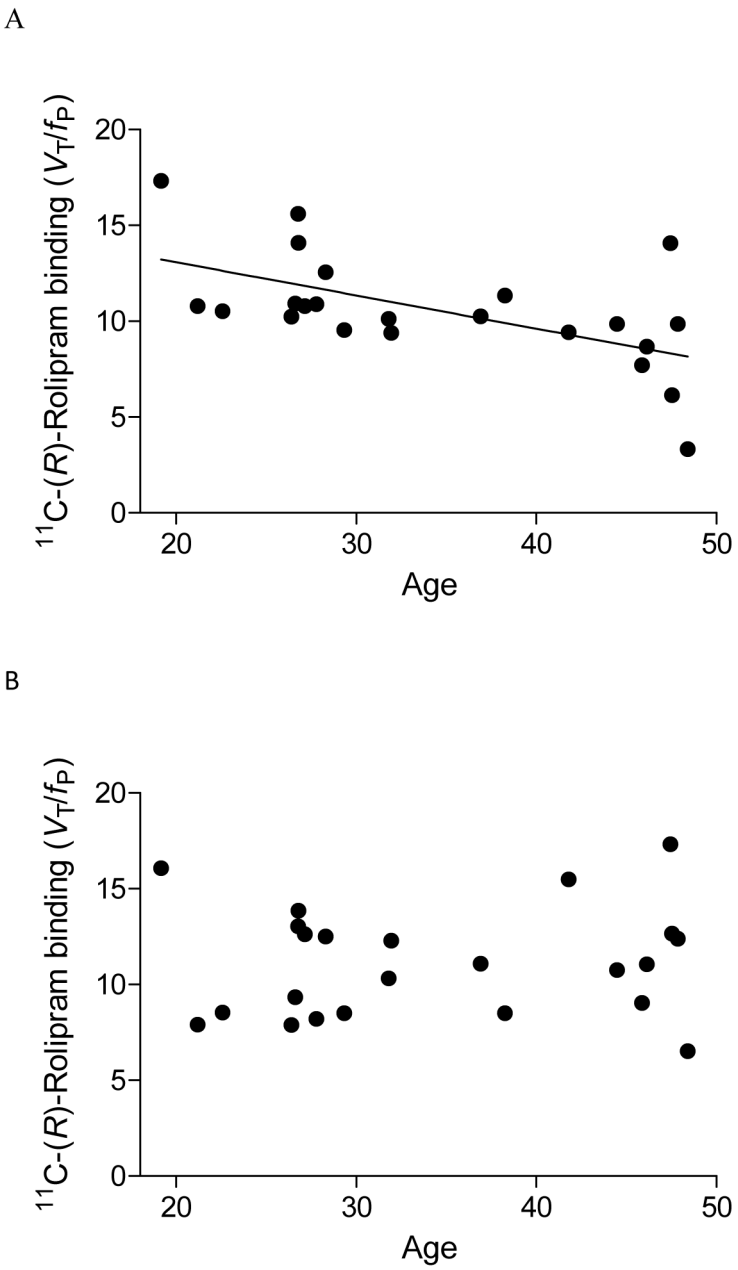

Figure 2.

Relationship between age and ^{11}C-(*R*)-rolipram binding levels before (A) and approximately eight weeks after starting treatment with a selective serotonin uptake inhibitor (SSRI) (B). A significant negative correlation between age and rolipram binding was observed under unmedicated conditions before starting SSRI (P=0.001–0.013, r=0.51–0.63 in 10 areas across brain; A). The significant correlation disappeared after starting SSRIs (P>0.39, r<0.19; B). This finding was due to older patients showing significantly greater increases in rolipram binding after SSRI. The graphs show average data across the 10 large brain regions.

Table 1

Demographic and clinical characteristics of the study sample

	Control (n=35)[1]	MDD (n=44)[2]	MDD with two PET (n = 23)
Females (n)	11 (31%)	12 (27%)	1 (4%)
Age	36 ± 11	38 ± 11	34 ± 10
Depression & anxiety ratings			
MADRS	0.7 ± 1.5	30 ± 6	30 ± 6[4]
$HDRS_{17}$	0.7 ± 0.9	20 ± 6	19 ± 5
HAM-A	0.7 ± 0.9	18 ± 7	20 ± 5
Age of onset	NA	19 ± 9	20 ± 9
Duration of current episode (months)	NA	67 ± 102	46 ± 54
Treatment naïve	NA	22	14
Length of time medication free (months) [range]	NA	28 ± 37 [0.5 – > 120]	15 ± 24 [0.7 – > 120]
Current comorbid anxiety disorders	0	20 (45%)	12 (52%)
Subjects with lifetime history of suicide attempts (n)	0	4	2
Prior exposure to antipsychotic agent (n)	0	1	0
Lifetime history of substance abuse (n)	0	4	3
Current cigarette smokers (n)	8 (23%)	10 (23%)[3]	5 (22%)[5]

[1] Includes 13 controls (31±10 years old, three females and 10 males) who had a second PET scan 8.0±2.1 weeks later without SSRI.

[2] Includes 23 patients who had two PET scans, before and after SSRI treatment, and 21 unmedicated patients who had only one PET scan.

[3] Includes four intermittent smokers. Six of the 10 subjects smoked cigarettes daily.

[4] Ratings before starting SSRI

[5] Includes two intermittent smokers.

No group difference was observed for age, gender balance, or percentage of cigarette smokers (P > 0.80).

Values are mean ± SD.

HAM-A: Hamilton Rating Scale for Anxiety; $HDRS_{17}$: Hamilton Rating Scale for Depression (17 item); MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; SSRI: selective serotonin reuptake inhibitor.