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The Selective Serotonin Reuptake Inhibitor Citalopram Decreases Human Immunodeficiency Virus Receptor and Coreceptor Expression in Immune Cells

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ABSTRACT

BACKGROUND: This study investigated whether the selective serotonin reuptake inhibitor (SSRI) citalopram downregulates the expression of the human immunodeficiency virus (HIV) receptor cluster of differentiation 4 (CD4) and coreceptors chemokine receptor type 5 and chemokine-related receptor type 4 (CCR5 and CXCR4) on peripheral blood mononuclear cells (PBMCs) and macrophages ex vivo as a potential mechanism of reducing susceptibility to HIV infection.

METHODS: The sample included 150 participants 18–58 years old (59% women, 65% African American, 61% with depression). Monocyte-depleted PBMCs were treated with phytohemagglutinin for 72 hours and then cultured in the presence of interleukin-2 with vehicle control or the SSRI (10^{-6} mol/L) for 2 hours. To generate monocyte-derived macrophages, monocytes were cultured for 7 days, after which either vehicle control or SSRI (10^{-6} mol/L) was added for 2 hours. RNA was collected from both cell types, and messenger RNA expression of CD4, CCR5, and CXCR4 was measured by real-time polymerase chain reaction.

RESULTS: In PBMCs, SSRI treatment decreased expression of CD4 ($p = .009$), CCR5 ($p = .008$), and CXCR4 ($p < .0001$). In monocyte-derived macrophages, SSRI treatment decreased expression of CD4 ($p < .0001$) and CXCR4 ($p = .0003$), but not CCR5 ($p = .71$). The suppressive effects of the SSRI on receptor expression did not differ as a function of depression diagnosis or depressive symptom severity.

CONCLUSIONS: Treatment with the SSRI at a physiologic dose decreased CD4, CCR5, and CXCR4 expression on PBMCs and macrophages ex vivo. These findings suggest that SSRI treatment, independent of depression status, downregulates HIV receptor and coreceptor expression and may reduce susceptibility of immune cells to HIV infection and decrease inflammation. If clinical trials confirm the present findings, ultimately there may be a role for using SSRI treatment adjunctively in HIV and acquired immunodeficiency syndrome.

Keywords: CCR5, CD4, CXCR4, Depression, HIV, SSRI

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Cell surface receptor expression on immune cells is implicated in the pathogenesis of human immunodeficiency virus (HIV) and many other medical conditions (1). For example, cluster of differentiation 4 (CD4) is a transmembrane glycoprotein found on the surface of several immune cells, including T helper cells, monocytes, macrophages, and dendritic cells (2,3). A member of the immunoglobulin superfamily, CD4 interacts with major histocompatibility complex (MHC) class II receptor involved in antigen presentation, signal transduction, and T cell activation in response to viral infection (2). In the context of HIV, the CD4 receptor and the chemokine-related receptor type 4 (CXCR4) function as coreceptors for viral entry into T helper cells—the primary mechanism leading to immune suppression and, ultimately, acquired immunodeficiency syndrome (AIDS) (4). Chemokine receptors, including CXCR4 and chemokine receptor type 5 (CCR5), play a broad role in viral pathogenesis, in part through the regulation of immune cell trafficking and effector functions (5). Although acute CXCR4 and CCR5 mediated responses to infection are adaptive, chronically elevated expression of these receptors on lymphocytes and macrophages may contribute to persistent immune activation and comorbid conditions, such as cardiovascular disease (5,6).

With chronic HIV infection, the widespread activation of T cells and monocytes/macrophages is associated with proinflammatory cytokine production, increased viral replication, and cellular immune activation, which, over time, leads to suppressed innate and adaptive immune function and susceptibility to opportunistic infections and cancers (4). Moreover, persistent immune activation can promote proinflammatory processes

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involved in atherosclerotic cardiovascular disease and neurocognitive impairment, both of which are highly prevalent in HIV/AIDS (4,7). Although CD4, CCR5, and CXCR4 receptors normally function to help immune cells identify and eradicate viruses, these receptors may be related to the pathogenesis of disease characterized by chronic immune activation and inflammation, including HIV (8–11). By extension, drugs that downregulate CD4, CCR5, and CXCR4 receptors could potentially modify HIV entry and replication as well as chronic immune activation and systemic inflammation.

Serotonin (5-hydroxytryptamine [5-HT]) receptors and the 5-HT transporter are widely distributed on monocytes, macrophages, T cells, and possibly natural killer (NK) cells (12). Thus, serotonin and serotonin-modulating agents may have a direct effect on innate and cellular immunity, which are critical pathways in host defense against viral pathogens, including HIV. Serotonin enhances the cytolytic activity of NK cells, possibly through 5-HT_{1A} receptors on monocytes (13,14), and may protect the function of NK cells (13). Serotonin also activates 5-HT receptors on T cells, suggesting potential effects on cellular activation, signal transduction, and cell surface receptor expression (15). Additional studies (16–18) suggested similar serotonin upregulation of T cell function in HIV infection. Thus, drugs affecting the serotonin system, including selective serotonin reuptake inhibitors (SSRIs), may regulate innate and adaptive immune function (19,20).

We previously showed that SSRI treatment ex vivo exerts numerous immune effects pertinent to the control of HIV infection, including 1) enhanced NK cytolytic activity that is involved in directly killing HIV-infected cells (21), 2) reduced infection of macrophages (22), and 3) decreased HIV replication in latently infected T cell and macrophage cell lines (22). Across these previous studies, SSRI effects were independent of depression status, suggesting a direct immunomodulatory effect of blocking serotonin reuptake regardless of depression diagnosis or depressive symptom severity. Because depression has been associated with immune dysregulation (23–33) and accelerated HIV disease progression (34–48), SSRIs could conceivably enhance mood and help restore innate and cell-mediated immunity simultaneously for patients with comorbid depression and HIV infection. However, it is unknown whether SSRIs could also have an antiviral effect via blocking the expression of the HIV receptor CD4 and coreceptors CCR5 and CXCR4, which are needed for cell entry.

To our knowledge, this is the first study to assess the effect of a SSRI (citalopram) on the expression of cell surface receptors (CD4, CCR5, CXCR4) ex vivo. Based on our prior work and a review of coreceptor biology, we hypothesized that SSRI would downregulate receptor expression across two types of immune cells implicated in HIV pathogenesis—T lymphocytes and monocyte-derived macrophages (MDMs).

METHODS AND MATERIALS

Subjects

To achieve a representative sample of adults with and without depression, subjects were recruited from organizations focusing on depression treatment in the University of Pennsylvania Health System and the surrounding Philadelphia community via community outreach presentations, clinician referrals, response to flyers, and word of mouth. Subjects were included if they were 18–65 years old, male or female, of any race or ethnicity, and able to communicate in English. Subjects with depression had current depressive symptoms (17-item Hamilton Depression Rating Scale [HDRS] score $\geq$8) and a diagnosis of either major depression or nonmajor depression, which included dysthymia or adjustment disorder with depressed mood. Subjects were excluded if they 1) had HIV infection; 2) had acute suicidal ideation and intent; 3) met diagnostic criteria for active substance dependence or abuse within the 12 months before enrollment; 4) used medication known to alter immune function within 4 weeks before enrollment or had a history of immunomodulatory therapy; 5) had active psychotic symptoms; 6) were currently taking pharmacotherapy for any psychiatric disorder, including any antipsychotic, antidepressant, antimanic, or anxiolytic medication, within 4 weeks before evaluation (for the antidepressant fluoxetine, subjects were excluded if fluoxetine had been used within 8 weeks before study enrollment); 7) were pregnant or nursing; 8) had significant chronic systemic illness; or 9) had hemoglobin $\leq$12.5 g/dL or hematocrit $\leq$38% (American Red Cross blood donor criteria). The same inclusion and exclusion criteria were used for nondepressed control subjects except that they did not have a Structured Clinical Interview for DSM diagnosis of depression and they had a 17-item HDRS score $\leq$7.

Procedures

Each subject received a comprehensive medical and psychiatric assessment, including medical history, review of systems, and physical examination including a standardized neurologic examination. Current and lifetime DSM-IV Axis I diagnoses were assessed by a research psychiatric clinician with a modified Structured Clinical Interview for DSM-IV (49). Consensus diagnoses were evaluated and determined at diagnostic conferences. Depression symptom severity was evaluated with the 17-item HDRS (50).

To control for potential circadian effects on immunity, subjects were studied at the same time of day, as in our previous studies (21,22). Subjects were placed in a recumbent position, an intravenous line was started at approximately 8:30 AM, and blood was drawn 30 minutes later following an acclimation period (27).

Receptor and Coreceptor Assessment

Peripheral whole blood was drawn from each subject. Within 1 hour of collection, peripheral blood mononuclear cells (PBMCs) were isolated by standard Ficoll-Paque separation technique (GE Healthcare, Piscataway, New Jersey). Monocytes were isolated from total PBMCs by our well-established adherence to plastic technique (51).

Monocytes were incubated for 7 days to generate MDMs in 48-well plates, 250,000 cells per well in Dulbecco's Modified Eagle's Medium (Gibco/Life Technologies, Grand Island, New York), 10% fetal bovine serum. After 7 days, one subset of MDMs received active SSRI (10^{-6} mol/L, a physiologic concentration) (52,53), and the other subset was treated with

the nonactive SSRI diluent (pure sterile water). After 2 hours of incubation with SSRI or diluent, total RNA was extracted using an RNeasy kit (Qiagen, Valencia, California).

Monocyte-depleted PBMCs were incubated with phytohemagglutinin (PHA; 7.5 μg/mL) for 3 days and then washed and cultured using well-established techniques (54–56) in 48-well plates, 1,000,000 cells per well, in Roswell Park Memorial Institute Medium (Gibco/Life Technologies), 10% fetal bovine serum supplemented with interleukin-2 (29 units/mL). One subset of PBMCs received active SSRI (10^{-6} mol/L), and the other subset received nonactive SSRI diluent (pure sterile water). After 2 hours of incubation with SSRI or diluent, total RNA was extracted using an RNeasy kit.

The expression of HIV receptor (CD4) and chemokine coreceptors (CCR5 and CXCR4) was determined using real-time polymerase chain reaction (57). Total RNA was treated with RNase free DNase (Gibco/Life Technologies) and reverse transcribed (1 μg) using an AffinityScript QPCR cDNA synthesis kit (Agilent Technologies, Santa Clara, California) with random primer, all as instructed by the manufacturer. One-tenth of the resulting complementary DNA was used as a template for real-time polymerase chain reaction amplification using MyiQ iCycler system (Bio-Rad Laboratories, Inc., Hercules, California). The sequences of the primers and probes used in this study are listed elsewhere (57). All primers and probes were synthesized by Integrated DNA Technologies, Inc. (Coralville, Iowa). The polymerase chain reaction fragments were cloned into pGEM-T vector (Promega, Madison, Wisconsin) and used to generate standard curves for corresponding genes. The expression of glyceraldehyde-3-phosphate dehydrogenase was used for normalization of gene expression (58). All amplification reactions were performed in duplicate, and an average messenger RNA (mRNA) quantity was expressed as copy number per 1000 copies of glyceraldehyde-3-phosphate dehydrogenase. The specificity of the amplification with SYBR Green (Bio-Rad Laboratories, Inc.) was confirmed by dye dissociation curve.

Statistical Analysis

The CD4, CCR5, and CXCR4 receptor mRNA expression was measured under a control condition and under a physiologic dose of SSRI for each of two cell types (PBMC/T cells and MDMs). For each response within each cell type, we used linear mixed models to accommodate within-subject correlations of these repeated responses across drug treatment conditions. We used $\log^{10}$ transformation of the coreceptor expression responses to reduce levels of skewness to appropriate levels for linear mixed model analyses. Each statistical model analyzed the main effect of SSRI, the main effect of depression diagnosis, and the interaction between SSRI treatment and depression diagnosis as predictors of HIV receptor and coreceptor expression within each cell type. To adjust for multiple comparisons across three dependent variables (CD4, CCR5, and CXCR4), we used an adjusted critical α level of $p = .017$.

The sample included 150 participants. The age range was 18–58 years (mean 32.09 years, SD 10.78). Most subjects were female (59%), African American (65%), and depressed (61%). The depressed group comprised individuals with major depression ($n = 86$), and nonmajor depression ($n = 6$), including dysthymia ($n = 2$) and adjustment disorder with depressed mood ($n = 4$). The depressed and nondepressed groups did not differ on mean (SD) age [depressed group, 33 years (11); nondepressed group, 34 years (12); $p = 1.00$], sex (depressed group, 40% male; nondepressed group, 43% male; $p = .73$), or race (depressed group, 64% African American; nondepressed group, 66% African American; $p = .86$). The 17-item HDRS score was 0–32 in the full sample, with a mean (SD) of 12.55 (9.24). By design, depression symptom severity was higher for the depressed group [mean HDRS = 18.39 (4.64)] than the nondepressed group [mean HDRS = 1.40 (1.62); $p < .0001$]. Because some subjects did not provide a sufficient volume of blood for the ex vivo experiments, sample sizes in the statistical models were 139–149.

RESULTS

Effect of SSRI on HIV Receptor and Coreceptor Expression in PBMCs

As shown in Figure 1, there was a significant suppressive effect of SSRI treatment on receptor and coreceptor expression in PBMCs. For CD4 expression, the mean log10 responses were 2.47 for vehicle control and 2.44 for SSRI ($F_{1,146} = 7.05$, $p = .0088$). For CCR5 expression, the mean log10 responses were 1.68 for vehicle control and 1.64 for SSRI ($F_{1,146} = 7.35$, $p = .0075$). For CXCR4 expression, the mean log10 responses were 2.79 for vehicle control and 2.75 for SSRI ($F_{1,148} = 20.19$, $p < .0001$).

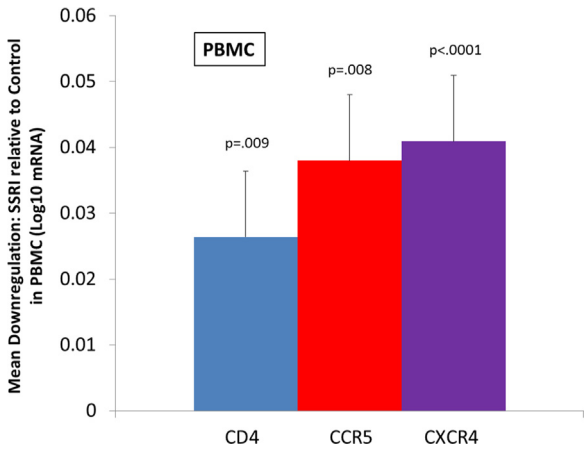

Figure 1. Ex vivo effect of selective serotonin reuptake inhibitor (SSRI) on cluster of differentiation 4 (CD4), chemokine receptor type 5 (CCR5), and chemokine-related receptor type 4 (CXCR4) receptor expression on peripheral blood mononuclear cells (PBMC) from adults with and without depression. Monocyte-depleted PBMC were immediately incubated with phytohemagglutinin for 3 days and then washed and cultured in the presence of interleukin-2. The vertical bars represent the distribution of within-subject differences in mRNA receptor expression (log10 scale) measured using real-time polymerase chain reaction after 2 hours of incubation with SSRI at a physiologic concentration (10^{-6} mol/L) compared with diluent (pure sterile water).

Effect of SSRI on HIV Receptor and Coreceptor Expression in MDMs

A similar pattern of HIV receptor and coreceptor expression findings emerged for MDMs (Figure 2). For CD4 expression, the mean log10 responses were 3.24 for vehicle control and 3.13 for SSRI ($F_{1,138} = 48.26$, $p < .0001$). For CCR5 expression, the mean log10 responses were 2.62 for vehicle control and 2.62 for SSRI ($F_{1,139} = .13$, $p = .71$). For CXCR4 expression, the mean log10 responses were 2.62 for vehicle control and 2.57 for SSRI ($F_{1,140} = 14.06$, $p = .0003$).

Effects of Depression on HIV Receptor and Coreceptor Expression in PBMCs and MDMs

There were no significant interactions between SSRI treatment condition and depression status for any of the three receptor expression variables across the two cell types. Depression status was tested as a main effect. In PBMCs, depression diagnosis was independently associated with lower expression of CD4 (log10 response = 2.39 for depressed group vs. 2.53 for nondepressed group, $t = 2.56$, $df = 146$, $p = .011$) and CXCR4 (log10 response = 2.70 for depressed group vs. 2.84 for nondepressed group, $t = 2.97$, $df = 148$, $p = .003$). However, the effect of depression diagnosis on CCR5 in PBMCs was not statistically significant. In MDMs, the main effect of depression diagnosis was nonsignificant for all three receptors. There were no significant interactions between depression severity (HDRS) and SSRI treatment in the depressed group. Correlation values between HDRS scores and expression level of the three receptors all were negative, regardless of cell type or SSRI treatment or vehicle control. None of the correlations between HDRS score and CD4 expression were significant (all p values $> .20$). The correlations between HDRS score and CCR5 expression were significant for SSRI treatment ($r = -.24$, $p = .003$) and vehicle control ($r = -.31$, $p = .022$) conditions for PBMCs and nonsignificant in MDMs, regardless of treatment condition (p values $> .10$). The correlations between HDRS score and CXCR4 were significant ($-.29 < r - .35$, p values $< .01$) regardless of treatment condition and cell type.

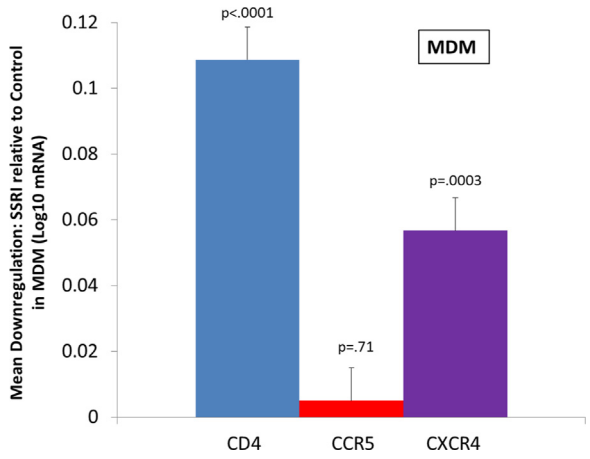

Figure 2. Ex vivo effect of selective serotonin reuptake inhibitor (SSRI) on cluster of differentiation 4 (CD4), chemokine receptor type 5 (CCR5), and chemokine-related receptor type 4 (CXCR4) receptor expression on monocyte-derived macrophages (MDM) from adults with and without depression. The vertical bars represent the distribution of within-subject differences in messenger RNA (mRNA) receptor expression (log10 scale) measured using real-time polymerase chain reaction after 2 hours of incubation with SSRI at a physiologic concentration (10^{-6} mol/L) compared with diluent (pure sterile water).

Covariate Analyses: Effects of Potentially Confounding Demographic Variables

Adjustment for age, sex, and race had no effect on the analyses of SSRI treatment, depression diagnosis, and treatment by diagnosis interaction effects. Nonsignificant effects of demographic covariates were found across both cell types and across all three coreceptors. Specifically, there were no significant interactions between SSRI treatment and depression diagnosis, age, sex, or race. For PBMCs, interaction p values were $> .17$ for CD4, $> .22$ for CCR5, and $> .37$ for CXCR4. For MDMs, interaction p values were $> .16$ for CD4, $> .32$ for CD4, and $> .16$ for CXCR4. Thus, effects of SSRI on receptor and coreceptor expression were independent of demographic variables.

DISCUSSION

To our knowledge, these findings are the first that show a SSRI can suppress expression of CD4, CCR5, and CXCR4 receptors on immune cells in an ex vivo model. Specifically, the SSRI citalopram at a physiologic dose (52,53) significantly decreased mRNA expression of all three cell surface receptors studied in PBMCs and in two of three cell surface receptors in MDMs (CD4, CXCR4). These findings support the hypothesis that SSRI treatment may exert a direct biological effect on receptor expression, suggesting a potentially novel biological pathway through which a SSRI could reduce HIV entry into T cells and macrophages and possibly limit viral infectivity.

Our findings are consistent with a prior in vitro study, which found that 5-HT decreased acute HIV replication by down-regulating CCR5 and by increasing secretion of the HIV suppressive chemokine macrophage inflammatory protein 1 (59). Those in vitro findings on the direct effects of serotonin are consistent with our previous finding of the direct effects of the SSRI citalopram on decreasing HIV infectivity of human macrophages in an acute ex vivo model as well as a chronic model of a T cell line and a macrophage cell line (22). Furthermore, there is clinical evidence of antiviral activity of SSRIs in the central nervous system. Letendre *et al.* (60) reported that individuals taking SSRIs (citalopram, sertraline, or trazodone) were more likely to have lower HIV viral loads in cerebrospinal fluid and better neuropsychological performance. Moreover, two clinical studies by Irwin *et al.* (61,62) demonstrated that SSRI treatment boosts baseline and vaccine-stimulated varicella-zoster virus specific immunity in patients with depression, further supporting the potential effect of antidepressant medication on clinically relevant markers of immune function. In addition, more recent studies also demonstrated anti-inflammatory effects of SSRIs in microglia (63,64). Relatedly, significant decreases in serotonin concentrations were found in the cerebrospinal fluid of HIV-seropositive individuals (65). Thus, serotonin and SSRIs may regulate central and peripheral immune system function, potentially benefiting individuals with HIV (19,20). The present study, in the context of prior work, is consistent with the

possibility that SSRI treatment may exert an immunoprotective effect, involving a combination of innate immunity and direct antiviral activity at the cellular level.

We speculate that SSRIs may inhibit HIV entry and replication in T cells and monocytes/macrophages by binding to the serotonin transporter, resulting in increased extracellular 5-HT concentrations. The change in 5-HT concentrations may downregulate expression of CD4 receptor and CXCR4 and CCR5 coreceptors, reducing HIV entry. In addition, 5-HT may augment the release of chemokines (CCL3, CCL4, and CCL5) from NK/$CD8^+$ cells, monocytes/macrophages, and T cells. These anti-HIV chemokines block CD4, CCR5, and CXCR4 receptors, further limiting HIV infectivity (66). The possibility of such direct molecular biological effects of SSRIs on immune function awaits further investigation.

Consistent with our previous ex vivo studies (21,22), the immune effects of the SSRI in this study were observed in subjects with and without depression. Specifically, there was no interaction between SSRI treatment of cells and participants' depression diagnostic status. Moreover, after adjusting for depression diagnosis, the effects of the SSRI on receptor expression remained significant. Additionally, no significant effect of depression diagnosis on CD4, CCR5, or CXCR4 expression in MDMs or CCR5 expression in PBMCs was found. Depression diagnosis was associated with greater suppression of CD4 and CXCR4 in PBMCs. However, PBMCs obtained from individuals with depression are known to have reduced lymphocyte proliferation in response to mitogen stimulation (32,33,67). Therefore, it is likely that the lower levels of receptors observed in PBMCs of individuals with depression were a consequence of decreased response to PHA stimulation and reduction of lymphocyte cell numbers. In contrast, MDM differentiation does not require PHA stimulation, and we did not observe any effects of depression diagnosis in MDMs. Just as there were no interactions between SSRI effects and depression diagnosis, there were no interactions between depression severity and SSRI effects in the subjects with depression. Although no effects of depression diagnosis on MDM receptors were observed, depression severity was associated with a decrease in CXCR4 receptor expression; in contrast to PBMCs, this was not related to PHA stimulation. Rather, it is well known that depression is associated with increased proinflammatory cytokines (30,33,68,69). Proinflammatory cytokines promote M1 polarization of macrophages, and M1 polarization is associated with reduced production of CXCR4 receptors (70). This mechanism could account for the effect of depression severity seen in the CXCR4 receptor in MDMs.

This study had many strengths, including a large sample size, a carefully controlled ex vivo model for SSRI effects on cell surface receptor expression, and the analysis of two key cell types directly involved in HIV pathogenesis (T cells and macrophages). In addition, our immune assessment was standardized by performing all blood draws at the same time of day, following 30 minutes of recumbency, to avoid diurnal effects on immunity and possible nonspecific methodologic factors (71–73). Subjects were also excluded for medical comorbidities, current substance abuse, or recent use of psychotropic medications or other immunomodulatory drugs that could affect immune function. The study used a physiologic dose of SSRI (10^{-6} mol/L) to produce a similar exposure that would occur in vivo. The SSRI dose used in the present study was the same dose that significantly enhanced NK cell innate immunity in our previous ex vivo work with HIV-seropositive individuals (21).

This study also has some possible limitations. First, because most of our sample was African American, it is uncertain whether the effects of SSRI on receptor expression will generalize to all racial subgroups. Second, the experimental method involving PHA mitogen-stimulated proliferation of PBMCs to generate T cells may have resulted in less cell surface receptor expression for individuals with depression compared with individuals without depression. This limitation does not apply to MDMs, and as noted, the SSRI effects were independent of depression. Third, because this study used an ex vivo design with medically healthy adults, future studies are required to test whether the effects observed here can be demonstrated in vivo among HIV-seronegative and HIV-seropositive individuals with and without depression. Our prior work in HIV-seropositive women with and without depression found that SSRI treatment ex vivo exerted numerous immunomodulatory effects, including enhanced innate immunity (NK cytotoxicity), enhanced suppression of HIV replication in latently infected T cells by killer lymphocytes (NK/CD8), and decreased HIV infection of macrophages (21,22), suggesting that the effect of SSRI treatment on HIV receptor and coreceptor expression in HIV-seropositive individuals is plausible. Because mRNA, and not actual protein level, was used to measure receptor and coreceptor expression in this study, future studies should directly measure protein levels of cell surface receptor expression (e.g., using flow cytometry). Finally, future in vivo studies are also needed to investigate the role of various other SSRIs on cell surface receptor expression and on other measures of innate and adaptive immune function.

In conclusion, this study tested the effect of a SSRI (citalopram) on HIV receptor and coreceptor expression ex vivo using two cell types (PBMCs and MDMs). The results support a novel biological pathway through which SSRI treatment could conceivably inhibit HIV cell entry and replication—through downregulating CD4 expression and chemokine receptor expression (CCR5, CXCR4). Furthermore, given the role of CD4, CCR5, and CXCR4 receptor expression in many other diseases characterized by immune activation and inflammation, including atherosclerosis (5,6), the present data suggest the additional possibility that SSRI treatment could modify other inflammatory-related diseases; this is an area for future research. The current data together with our prior ex vivo investigations of HIV infection support the direct effect of SSRIs on immune regulation and viral control. Future studies, such as randomized clinical trials of SSRI effects on immune modulation, are needed to determine whether SSRI treatment decreases mRNA and protein levels of CD4, CCR5, and CXCR4 on immune cells in a sustained manner in vivo. If so, there may be a role for the clinical use of SSRIs adjunctively for immune restoration in HIV/AIDS in individuals with and without depression.

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The authors report no biomedical financial interests or potential conflicts of interest.

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