Decrease in Brain Serotonin 2 Receptor Binding in Patients With Major Depression Following Desipramine Treatment

A Positron Emission Tomography Study With Fluorine-18–Labeled Setoperone

Lakshmi N. Yatham, MBBS, FRCPC; Peter F. Liddle, PhD, MBBS; Joelle Dennie, MSc; I-Shin Shiah, MD; Michael J. Adam, PhD; Carol J. Lane, MSc; Raymond W. Lam, MD; Thomas J. Ruth, PhD

Background: The neuroreceptor changes involved in therapeutic efficacy of various antidepressants remain unclear. Preclinical studies have shown that long-term administration of various antidepressants causes down-regulation of brain serotonin 2 (5-HT2) receptors in rodents, but it is unknown if similar changes occur following antidepressant treatment in depressed patients. Our purpose, therefore, was to assess the effects of treatment with desipramine hydrochloride on brain 5-HT2 receptors in depressed patients using positron emission tomography (PET) and fluorine-18 (18F)–labeled setoperone.

Methods: Eleven patients who met DSM-IV criteria for major depression as determined by a structured clinical interview for DSM-III-R diagnosis and suitable for treatment with desipramine were recruited. Ten patients underwent a PET scan before and another after 3 to 4 weeks of treatment with desipramine.

Results: Eight of the 10 patients responded to desipramine treatment as indicated by more than 50% decrease in Hamilton Depression Rating Scale scores. Depressed patients showed a significant decrease in 5-HT2 receptor binding as measured by setoperone binding in frontal, temporal, parietal, and occipital cortical regions following desipramine treatment. The decrease in 5-HT2 receptor binding was observed bilaterally and was particularly prominent in frontal cortex.

Conclusions: Depressed patients showed a significant reduction in available 5-HT2 receptors in the brain following desipramine treatment, but it is unknown if this change in 5-HT2 receptors is due to clinical improvement or an effect of desipramine that is unrelated to clinical status.

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The mechanisms by which antidepressants exert their therapeutic effects in major depression have remained elusive. Since there is a time lag of about 2 to 4 weeks between initiating antidepressant treatment and the clinical response, it has been suggested that alterations in neurotransmitter receptors occurring within this time frame might be relevant to therapeutic effects of these drugs. Because 5-hydroxytryptamine (serotonin [5-HT]) has been implicated in depression,1,2 a number of animal studies4-15 have assessed the changes in 5-HT receptors after 2 to 4 weeks of the administration of antidepressants. Serotonin 2 receptors are the most widely studied,4,8,9,11-13 and these studies have shown that long-term administration of tricyclic antidepressants,4,8,9,11-13 monoamine oxidase inhibitors,4,6,8,12 atypical antidepressants such as imipramine4,6,8,12 and mianserin hydrochloride,7,8,12 and most but not all serotonin reuptake inhibitors4,9,12,16-19 decreases the density of cortical 5-HT2 receptors in rats. It is, however, unknown if antidepressant treatment would lead to similar changes in 5-HT2 receptor density in depressed patients.

The purpose of our study was to ascertain the effects of 3- to 4-week treatment with an antidepressant on brain 5-HT2 receptors using positron emission tomography (PET) in patients with major depression. Ligands such as carbon 11 (11C-(R)-(+)-4-(1-hydroxy-1-[2,3-dimethoxyphenyl]methyl)-N-[2-(4-fluorophenylethyl)]-piperidine (MDL 100 907),20 11C-N-methylspiperone,21 18F-setoperone,22 and 18F-altanserin23 are available for imaging 5-HT2 receptors in human brain.24 We chose 18F-setoperone because (1) it has a total-to-nonspecific binding ratio of greater than 2; (2) it was recommended by the European Task Force as a suitable ligand for imaging 5-HT2 receptors in human brain.24 We chose 18F-setoperone because (1) it has a total-to-nonspecific binding ratio of greater than 2; (2) it was recommended by the European Task Force as a suitable ligand for imaging 5-HT2 receptors in human brain.24 We chose 18F-setoperone because (1) it has a total-to-nonspecific binding ratio of greater than 2; (2) it was recommended by the European Task Force as a suitable ligand for imaging 5-HT2 receptors in human brain.24 We chose 18F-setoperone because (1) it has a total-to-nonspecific binding ratio of greater than 2; (2) it was recommended by the European Task Force as a suitable ligand for imaging 5-HT2 receptors in human brain.24 We chose 18F-setoperone because (1) it has a total-to-nonspecific binding ratio of greater than 2; (2) it was recommended by the European Task Force as a suitable ligand for imaging 5-HT2 receptors in human brain.24
SUBJECTS AND METHODS

SUBJECTS

Eleven patients who met DSM-IV criteria for major depressive disorder and who were suitable for treatment with desipramine were recruited from the University of British Columbia Hospital, Vancouver. The study was approved by the University Ethics Committee, and subjects gave written informed consent. The diagnosis of major depression was made using the Structured Clinical Interview for DSM-III-R. None had other Axis I diagnoses or current or past alcohol or substance abuse. All subjects were physically healthy as determined by history and results of physical examination. The severity of depression was quantified using the 21-item Hamilton Depression Rating Scale (HAM-D). All study subjects were free of psychotropic drugs for at least 2 weeks (5 weeks in the case of fluoxetine hydrochloride) before baseline PET scan, and none had ever received electroconvulsive therapy.

PET PROCEDURE

Radiosynthesis of [18F]-setoperone was accomplished by a modified method of Crouzel and colleagues, as described by Adam et al. Radioactivity in brain tissue was measured with a PET system (ECAT 933B/31; CTI/Siemens, Knoxville, Tenn). The spatial resolution of images is 6 mm (full width at half maximum). Subjects were supine with the head slightly tilted to obtain brain slices parallel to the canthomeatal line. Each subject had a 10-minute transmission scan for correcting PET images for attenuation. Following this, subjects were given 148 to 259 MBq of [18F]-setoperone intravenously, and a 15-frame scan was performed. The numbers and durations of frames were as follows: 5 frames for 2 minutes each, 4 frames for 5 minutes each, 4 frames for 10 minutes each, and 2 frames for 20 minutes each (total duration, 110 minutes).

RESULTS

One patient could not tolerate the side effects of desipramine and dropped out on day 4. The other 10 patients completed the study, and the data analysis is presented for these 10.

The subjects had a mean age of 40.6 ± 9.2 years. Three patients had no previous depressive episodes, and 2 had 1 previous episode. The other 5 patients had from 3 to 12 previous episodes of depression (Table 1). The duration of current depressive episode ranged from 20 to 120 weeks. Four patients had been free of psychotropic medication for more than 6 months, and 1 patient was drug naive. The other 5 patients were drug free from 2 to 5 weeks. Four patients had been free of psychotropic medication was allowed except lorazepam or oxazepam as required for night sedation. Subjects had a second PET scan 3 to 4 weeks after the commencement of desipramine therapy, 12 to 20 hours after the last dose.

TREATMENT

Each patient started desipramine hydrochloride therapy, 50 mg, and the dose was increased to 100 mg on day 4. Patients underwent assessment weekly with a clinical interview and a 21-item HAM-D. If there was no improvement in symptoms by the second week, the dose of desipramine hydrochloride was increased to 150 mg; a further increase in dose was made if no improvement was seen by the third week. No other psychotropic medication was allowed except lorazepam or oxazepam as required for night sedation. Subjects had a second PET scan 3 to 4 weeks after the commencement of desipramine therapy, 12 to 20 hours after the last dose.

DATA ANALYSIS

Using the multipurpose imaging (MPI) tool to define regions in frontal, temporal, and parietal cortex and cerebellum, we confirmed previous observations that cortical-to-cerebellar ratio is constant, indicating pseudoequilibrium, between 70 to 110 minutes after injection of [18F]-setoperone in depressed patients.

Statistical parametric mapping (SPM96) software was used to align PET images in the 70- to 110-minute period, to coregister them to magnetic resonance images, and to transform the magnetic resonance images (and PET images) into the standard coordinate frame used for templates in SPM96. Images were smoothed by applying a 12-mm (full width at half maximum) isotropic Gaussian filter to improve the signal-to-noise ratio.

For trace doses of setoperone at equilibrium, the amount of setoperone bound to receptors is proportional to the binding potential, \(B_{\text{max}}/K_d\), where \(B_{\text{max}}\) is the total number of receptors and \(K_d\) is the equilibrium-binding constant. To determine the binding potential from the measured concentration of setoperone in cerebral tissue, it is necessary to allow for variation in the amount of setoperone in plasma. This can be performed by comparing the setoperone concentration in the region of interest with that in a reference region. Provided the capacity for cation consistently has been shown to decrease the density of 5-HT2 receptors in rat studies.

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nonspecific binding is identical in the region of interest and the reference region, the ratio of setoperone concentration in the region of interest \(C_{\text{local}}\) to that in the reference region \(C_{\text{cerebellum}}\) is given using the following formula:

\[
C_{\text{local}}/C_{\text{cerebellum}} = fBP_{\text{local}} + 1,
\]

where \(BP_{\text{local}}\) is the local binding potential, and \(f\) is a quantity that reflects the total binding capacity (specific + nonspecific) in the reference region. Although cerebellum has been used as a reference region, Petit-Taboue et al.\(^3\) have demonstrated that in humans, nonspecific binding of setoperone in cerebellum is different from that in cortex. Hence this equation is not accurate, and its use leads to errors of approximately 20% in the estimation of \(fBP_{\text{local}}\) if cerebellum is used as a reference region. However, Petit-Taboue et al.\(^3\) demonstrated that nonspecific binding does not vary substantially between different cortical regions. Therefore, when the object is to measure regional changes in setoperone binding, an alternative approach is to use the whole cortex as the reference region.

The following equation is used when the whole cortex is treated as the reference region:

\[
f = 1/(BP_{\text{global}} + k5/k6),
\]

where \(BP_{\text{global}}\) is mean global binding potential, and \(k5\) and \(k6\) are the transfer coefficients for attachment to and detachment from nonspecific binding sites. If \(BP_{\text{global}} + k5/k6\) is not substantially affected by treatment, the change in \(C_{\text{local}}/C_{\text{cerebellum}}\) is proportional to the change in binding potential during treatment. If \(BP_{\text{global}} + k5/k6\) changes during treatment, change in \(C_{\text{local}}/C_{\text{global}}\) is proportional to change in ratio of local binding potential to mean global binding capacity (specific + nonspecific), but there is reduced power to detect local changes in binding potential in regions where local change is in the same direction as the mean global change. Provided there is no substantial change in global binding potential, it is preferable to use the whole cortex as the reference region for the determination of local changes, as this avoids errors due to differences between cortical and cerebellar nonspecific binding.

We evaluated \(C_{\text{global}}\) using the middle 10 slices of the image and \(C_{\text{cerebellum}}\) in a cerebellar region drawn using the MRI tool. The pretreatment value of the ratio \(C_{\text{global}}/C_{\text{cerebellum}}\) was 1.173, whereas the posttreatment ratio was 1.148 (paired \(t\), \(0.514; \text{P} = .62\)). The minimal observed change in the ratio \(C_{\text{global}}/C_{\text{cerebellum}}\) justifies the use of whole cortex as the reference region for determining local changes in setoperone binding.

Using SPM96, we then determined the change in ratio of local setoperone concentration to mean global setoperone concentration during treatment with proportional scaling. The threshold for including voxels in the analysis was set at 1.3 times mean global cerebral image intensity to exclude non–gray matter voxels. For each voxel, the general linear model was used to estimate the mean change in \(C_{\text{local}}/C_{\text{global}}\). The significance of the change for each voxel was determined applying the method developed by Worsley\(^3\) based on the theory of Gaussian fields, as implemented in SPM96.\(^3\)\(^\text{a}\) Although there are approximately 58,000 voxels in the image, the image intensity in adjacent voxels is strongly correlated, so that there are only about 90 independent measurements. In effect, Worsley’s method determines the number of independent measurements and applies the appropriate Bonferroni-type correction.\(^3\)\(^\text{a}\) Voxels in which the significance of \(z\) satisfies this correction can be accepted as significant irrespective of whether they are a part of a contiguous set of voxels exhibiting significant change.

The theory of Gaussian fields was also applied to determine the statistical significance of clusters of contiguous voxels in which change during treatment exceeded a specified threshold. For this calculation, we set the threshold of \(z = 1.96\) corresponding to \(P < .025\) one-tailed (or \(P < .05\) two-tailed). Worsley’s method\(^3\)\(^\text{a}\) calculates the significance of clusters, taking account of the extent and peak \(z\) value within the cluster, and then applies a correction allowing for the multiple comparisons performed. Cluster significance level was set at \(P < .05\).

Pearson correlations between changes in relative setoperone binding in the significant clusters and changes in 21-item HAM-D score and HAM-D suicide item score between pretreatment and posttreatment conditions were computed. Unless otherwise indicated, data are given as mean ± SD.

This is the first study to assess the effects of desipramine treatment on brain 5-HT\(_2\) receptors in living, depressed patients. The results indicated that depressed patients had a significant decrease in brain setoperone binding in various cortical areas, including frontal, temporal, parietal, and occipital regions, following desipramine treatment. The decrease in setoperone binding was observed bilaterally, with decreases highly significant in left medial and orbitomedial frontal gyri, left inferior frontal gyrus, left middle and inferior temporal gyri, right inferior frontal gyrus, right lingual gyrus, and right middle occipital gyrus.

Several interpretations must be considered for a decrease in setoperone binding in our study subjects. First, the methods used in our study would not permit an independent determination of \(B_{\text{max}}\) and \(K_d\). Hence, a decrease in setoperone binding observed following desipramine treatment in our study could be due to a decrease in \(B_{\text{max}}\) or an alteration in \(K_d\). However, postmortem stud-
ies of brain 5-HT2 receptors in depressed patients have shown a decrease in $B_{max}$ without any alteration in $K_d$ for 5-HT2 receptors.39-43 Similarly, studies of the effects of antidepressant treatments on brain 5-HT2 receptors in rodents also have shown a decrease in $B_{max}$ without a change in $K_d$ for 5-HT2 receptors.4,7,8,13,17,18 Therefore, the decrease in setoperone binding observed in depressed patients following desipramine treatment in this study is likely to be due to a decrease in $B_{max}$, indicating a decrease in 5-HT2 receptor density.

Second, although desipramine does not inhibit 5-HT reuptake, long-term treatment with desipramine might lead to an increase in brain 5-HT levels through some other mechanism. An increase in brain 5-HT levels could occupy 5-HT2 receptors, leaving a decreased number of receptors available for setoperone binding, thus account-

Table 1. Sociodemographic and Illness Characteristics for Depressed Patients Receiving Desipramine Treatment*

<table>
<thead>
<tr>
<th>Subject No./Sex</th>
<th>Age, y</th>
<th>No. of Previous Depressive Episodes</th>
<th>Duration of Current Episode, wk</th>
<th>Duration of Drug-Free Period</th>
<th>Pretreatment HAM-D Score</th>
<th>Posttreatment HAM-D Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F</td>
<td>49</td>
<td>4</td>
<td>78</td>
<td>Drug naive</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>2/M</td>
<td>46</td>
<td>12</td>
<td>50</td>
<td>5 wk</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>3/M</td>
<td>41</td>
<td>1</td>
<td>32</td>
<td>30 wk</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>4/M</td>
<td>34</td>
<td>0</td>
<td>120</td>
<td>4 wk</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>5/M</td>
<td>30</td>
<td>0</td>
<td>100</td>
<td>5 wk</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>6/F</td>
<td>47</td>
<td>10</td>
<td>70</td>
<td>&gt;1 y</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>7/M</td>
<td>47</td>
<td>10</td>
<td>70</td>
<td>2 wk</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>8/F</td>
<td>50</td>
<td>0</td>
<td>52</td>
<td>3 wk</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>9/F</td>
<td>40</td>
<td>7</td>
<td>26</td>
<td>26 wk</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>10/F</td>
<td>22</td>
<td>3</td>
<td>26</td>
<td>26 wk</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>All, mean ± SD</td>
<td>40.6 ± 9.2</td>
<td>3.8 ± 4.4</td>
<td>57.4 ± 34.0</td>
<td>. . .</td>
<td>27.0 ± 5.6</td>
<td>7.0 ± 7.8</td>
</tr>
</tbody>
</table>

*HAM-D indicates 21-item Hamilton Depression Rating Scale; ellipses, cannot be calculated. Desipramine was given as desipramine hydrochloride.

Table 2. Changes in Setoperone Binding During Desipramine Treatment in Depressed Patients

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Size</th>
<th>$z$ Score</th>
<th>Corrected $P$</th>
<th>Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 695</td>
<td>4.53</td>
<td>&lt;.001</td>
<td>.007</td>
<td>5.43</td>
</tr>
<tr>
<td>4.51</td>
<td>.008</td>
<td>.008</td>
<td>1.5626 ± 0.0514</td>
<td>1.3526 ± 0.0514</td>
</tr>
<tr>
<td>4.50</td>
<td>.008</td>
<td>.008</td>
<td>1.4617 ± 0.0590</td>
<td>1.3407 ± 0.0572</td>
</tr>
<tr>
<td>4.18</td>
<td>.03</td>
<td>.008</td>
<td>1.5003 ± 0.0941</td>
<td>1.3281 ± 0.0938</td>
</tr>
<tr>
<td>4.17</td>
<td>.03</td>
<td>.008</td>
<td>1.6116 ± 0.0403</td>
<td>1.3966 ± 0.0402</td>
</tr>
<tr>
<td>4.10</td>
<td>.04</td>
<td>.008</td>
<td>1.6981 ± 0.0538</td>
<td>1.4281 ± 0.0536</td>
</tr>
<tr>
<td>4.10</td>
<td>.04</td>
<td>.008</td>
<td>1.3829 ± 0.0971</td>
<td>1.2440 ± 0.0971</td>
</tr>
<tr>
<td>4.08</td>
<td>.04</td>
<td>.008</td>
<td>1.3316 ± 0.0313</td>
<td>1.2237 ± 0.0310</td>
</tr>
<tr>
<td>4.08</td>
<td>.04</td>
<td>.008</td>
<td>1.3451 ± 0.0723</td>
<td>1.2192 ± 0.0721</td>
</tr>
<tr>
<td>4.04</td>
<td>.05</td>
<td>.008</td>
<td>1.6257 ± 0.0338</td>
<td>1.4290 ± 0.0338</td>
</tr>
</tbody>
</table>

*18F-setoperone indicates fluorine 18–labeled setoperone. Desipramine was given as desipramine hydrochloride.
†Coordinates are in millimeters from the origin at the midpoint of anterior commissure, in the coordinate frame employed in statistical parametric mapping.

Figure 1. Statistical parametric maps of t values displayed as projections on the sagittal (A), transverse (B), and coronal (C) renderings of the brain. These projections illustrate regions of decreased binding of fluorine 18–labeled setoperone following desipramine hydrochloride treatment.
ing for a decreased binding we observed. However, a recent PET study\textsuperscript{44} using \textsuperscript{18}F-setoperone reported no significant change in 5-HT\textsubscript{2} receptor binding following an acute challenge dose of paroxetine, the most potent 5-HT reuptake inhibitor in healthy subjects. This would suggest that elevation in 5-HT levels has no measurable impact on 5-HT\textsubscript{2} receptor binding as assessed with PET, thus suggesting that decreased setoperone binding observed in the study subjects is not due to a confounding effect of elevation in endogenous brain 5-HT levels.

Third, since patients underwent scanning while receiving treatment with desipramine, we cannot exclude the possibility that the decrease in setoperone binding is due to desipramine binding to 5-HT\textsubscript{2} receptors and not due to a decrease in 5-HT\textsubscript{2} receptor density. However, this is unlikely, because desipramine binding would be expected to occur wherever there are 5HT\textsubscript{2} receptors, but we observed no substantial global change in setoperone binding.

Our study has some limitations. First, although setoperone binds with higher affinity to 5-HT\textsubscript{2A} receptors ($K_i = 0.37$ nmol/L),\textsuperscript{34} it also has some affinity ($K_i = 50$ nmol/L) to 5-HT\textsubscript{2C} receptors,\textsuperscript{45} and hence we cannot tell whether a reduction in binding observed is due to a down-regulation of 5-HT\textsubscript{2A} or 5-HT\textsubscript{2C} or both receptor populations. Second, most patients in our study improved by the time the second PET scan was performed. Hence, we cannot tell if the decrease in 5-HT\textsubscript{2} receptor binding is due to clinical improvement that may or may not have been induced by desipramine or due to an effect of desipramine that was unrelated to clinical improvement. The fact that all 10 patients showed a reduction in 5-HT\textsubscript{2} receptor binding but only 8 improved substantially supports the latter possibility. Conversely, in a preliminary PET study,\textsuperscript{46} we reported that electroconvulsive therapy, another effective treatment for depression, induced a significant decrease in 5-HT\textsubscript{2} receptor binding in all 6 depressed patients who improved, supporting the former possibility.

Based on our finding of a decrease in 5-HT\textsubscript{2} receptor binding following desipramine treatment, one would expect an increase in 5-HT\textsubscript{2} receptor binding to be associated with depression. In this regard, several\textsuperscript{39-42,47} al-

Figure 2. Areas of significant decreases in fluorine 18–labeled setoperone binding on the sagittal renderings of the brain indicated by arrows (A, left inferior temporal gyrus; B, left middle temporal gyrus and left inferior frontal gyrus; C, left medial frontal gyrus; D, right lingual gyrus; E, right middle occipital gyrus and right inferior frontal gyrus; and F, right inferior frontal gyrus) in depressed patients following desipramine hydrochloride treatment.
though not all\textsuperscript{44-45} postmortem studies that examined 5-HT\textsubscript{2} receptor binding in brain samples from suicides reported increased $B_{\text{max}}$ with no changes in $K_{d}$ in various brain regions, particularly in frontal cortex, compared with control subjects. Similarly, 5-HT\textsubscript{2} receptor binding was also reported to be increased in postmortem brain samples of depressed patients who died of natural causes, compared with controls.\textsuperscript{46} Of the 2 studies that assessed brain 5-HT\textsubscript{2} receptor density in living, depressed patients, the single-photon emission tomography scan study with 2-iodine 123-ketanserin reported an increase in $B_{\text{max}}$ within parietal cortex and right inferior frontal region,\textsuperscript{33} whereas the PET study by Biver et al\textsuperscript{34} using \textsuperscript{11}C-ketanserin reported a decrease in 5-HT\textsubscript{2} receptor binding in the right postrolateral orbitofrontal cortex and anterior insular cortex in depressed patients compared with controls. The discrepancy in findings between the latter study and previous single-photon emission tomography and postmortem studies that showed an increased 5-HT\textsubscript{2} receptor binding in depression might be related to differences in duration of drug-free periods before ascertaining 5-HT\textsubscript{2} receptor binding.

In conclusion, to our knowledge, we demonstrated for the first time in humans that depressed patients show a decrease in brain 5-HT\textsubscript{2} ligand binding following desipramine treatment. Our results, however, cannot tell us whether the decrease in 5-HT\textsubscript{2} receptor binding was related to clinical improvement or to an effect of desipramine that was unrelated to clinical status. Further studies assessing the effects of antidepressant treatment on brain 5-HT\textsubscript{2} receptors in depressed patients are needed to verify the hypothesis that 5-HT\textsubscript{2} receptors are an important target for antidepressant therapies.

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Reprints: Lakshmi N. Yatham, MBBS, FRCP(C), Mood Disorders Clinical Research Unit, The University of British Columbia, 2255, Wesbrook Mall, Vancouver, British Columbia, Canada V6T 2A1 (e-mail: yatham@unixg.ubc.ca).

REFERENCES

5. Peroutka SJ, Snyder SH. Regulation of serotonin-2 (5-HT\textsubscript{2}) receptors labeled with \textsuperscript{11}C-spiroperidol by chronic treatment with the antidepressant amitriptyline. J Pharmacol Exp Ther. 1980;215:582-587.


29. Arango V, Ernsberger P, Marzuk PM, Chen JS, Tierney H, Stanley M, Reis DJ, Mann JJ. Autoradiographic demonstration of increased serotonin 5-HT2 and \(\beta\)-adrenergic receptor binding sites in the brain of suicide victims. *Arch Gen Psychiatry*. 1990;47:1038-1047.


42. Arango V, Ernsberger P, Marzuk PM, Chen JS, Tierney H, Stanley M, Reis DJ, Mann JJ. Autoradiographic demonstration of increased serotonin 5-HT2 and \(\beta\)-adrenergic receptor binding sites in the brain of suicide victims. *Arch Gen Psychiatry*. 1990;47:1038-1047.


47. Arango V, Ernsberger P, Marzuk PM, Chen JS, Tierney H, Stanley M, Reis DJ, Mann JJ. Autoradiographic demonstration of increased serotonin 5-HT2 and \(\beta\)-adrenergic receptor binding sites in the brain of suicide victims. *Arch Gen Psychiatry*. 1990;47:1038-1047.


50. Arango V, Ernsberger P, Marzuk PM, Chen JS, Tierney H, Stanley M, Reis DJ, Mann JJ. Autoradiographic demonstration of increased serotonin 5-HT2 and \(\beta\)-adrenergic receptor binding sites in the brain of suicide victims. *Arch Gen Psychiatry*. 1990;47:1038-1047.

51. Arango V, Ernsberger P, Marzuk PM, Chen JS, Tierney H, Stanley M, Reis DJ, Mann JJ. Autoradiographic demonstration of increased serotonin 5-HT2 and \(\beta\)-adrenergic receptor binding sites in the brain of suicide victims. *Arch Gen Psychiatry*. 1990;47:1038-1047.


