Serotonin modulation of cerebral glucose metabolism in normal aging

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Abstract

Age-related alterations in serotonin function may increase the vulnerability to psychiatric and neurodegenerative disorders in late life. The neuroendocrine and cerebral metabolic response to the acute administration of the selective serotonin reuptake inhibitor, citalopram (40 mg, IV), was measured in 17 normal control subjects using positron emission tomography (PET) to evaluate changes in serotonin function with normal aging. The citalopram-induced change in cerebral metabolism was positively correlated with age in the right precuneus, right paracentral lobule, and left middle temporal gyrus and negatively correlated with age in the left anterior cingulate gyrus, right inferior and middle frontal gyri, right insula, and right inferior parietal lobule. The positive correlations in mainly posterior brain regions indicate that normal aging is associated with an increase in metabolism after citalopram administration, whereas the negative correlations in mainly anterior brain regions indicate that normal aging is associated with a greater decrease in metabolism. These results suggest different compensatory processes in anterior compared to posterior brain regions secondary to the age-related loss of serotonin innervation.

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1. Introduction

Age-related declines in the functional integrity of the serotonin (5-HT) system have been demonstrated in animal studies (e.g. [3,9,13]), human in vivo neuroimaging studies, and analyses of the brain at post-mortem examination (e.g. [2,23,35]). These age-related alterations in the serotonin system may have implications for the pathophysiology of psychiatric disorders in late life, including depression and psychosis, as well as the occurrence of these symptoms in neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases (e.g. [16,26]). The majority of post-mortem and in vivo imaging studies have focused upon the serotonin transporter and the 5-HT 1A and 5-HT 2A receptors. These findings have been reviewed previously [19]; therefore, we will refer to recent studies, most of which reported decreases in binding to these sites (e.g. [2,34]). While neuroimaging studies have been fairly consistent in reporting age-related declines in serotonin transporter binding (e.g. [15,25]), neurochemical analyses of the brain at post-mortem examination have not found age-related alterations in transporter binding (e.g. [1,32]). Serotonergic neurons located intrinsic and extrinsic to the hypothalamus are involved in pituitary hormone secretion [22]; thus, the neuroendocrine response to administration of serotonin agonists, such as fenfluramine or ipsapirone, can be used to evaluate central serotonergic function. Studies have demonstrated a decreased neuroendocrine response with increasing age and provide evidence of age-related changes in central serotonergic function (e.g. [11,17]). The goal of the present study was to examine the effect of age on central serotonin function using a paradigm that we have developed to measure the cerebral glucose metabolic response to the acute administration of the selective serotonin reuptake inhibitor (SSRI), citalopram (Celexa)
Previous studies have not demonstrated the sensitivity of serotonin receptor radiotracers to pharmacologically induced alterations in serotonin concentrations [21,29]. Therefore, the method used in the present study is the most direct strategy for measuring serotonin function in vivo that is currently available. Citalopram was used in these studies as it is the most pharmacologically selective of the SSRIs and is well-tolerated in intravenous form across the life-span [31]. In the present study, measures of plasma prolactin and cortisol values were also obtained to provide an indirect measure of serotonin function for comparison with previous neuroendocrine challenge studies (e.g. [17]).

In a previous study using the same paradigm in young normal controls, citalopram administration significantly reduced metabolism in right cortical regions (cingulate, superior and middle frontal, parietal and superior occipital cortices), the left thalamus, and the right cerebellum. Increases in cerebral glucose metabolism were observed in the left temporal and occipital cortices [31]. Time-dependent increases in cortisol and prolactin were observed after citalopram administration. Due to evidence of diminished serotonergic responsivity with increasing age, we hypothesized that there would be age-related differences in glucose metabolism in regions identified in the previous study [31]. Specifically, we hypothesized that the cerebral metabolic response to citalopram would be blunted in normal aging, consistent with a decrease in serotonin innervation with age. We further hypothesized that the neuroendocrine response to citalopram administration would be blunted in normal aging, consistent with the neuroimaging results.

2. Methods

2.1. Study design

Seventeen subjects (8 males, 9 females, mean age 41 ± 17 [range 21-70] years) were studied. Positron emission tomography (PET) scans of cerebral glucose metabolism were performed on two consecutive days after administration of placebo (saline) or citalopram (40 mg, IV, infused over 1 h). Plasma concentrations of cortisol and prolactin were also determined at baseline and for two hours after the end of the infusion.

2.2. Subject screening and selection

Subjects were recruited through advertisements in the community. Prior to the PET scans, subjects underwent psychiatric evaluation (including a structured clinical interview, SCID [7], laboratory testing (including CBC and blood chemistry), toxicology screening and magnetic resonance (MR) imaging scans (GE 1.5 T). Subjects were excluded from the study based upon a history of or current psychological or neurological disorder or substance abuse. Subjects who were not medically stable (including a current diagnosis of diabetes not controlled by diet) as well as those taking prescription or over-the-counter medications with central nervous effects during the past month were also excluded. After subjects were presented with a complete description of the study, written informed consent was obtained according to procedures established by the Institutional Review Board and the Radiation Safety Committee of the North Shore-Long Island Jewish Health System.

2.3. Citalopram administration

The radiotracer was injected after a mean pre-treatment interval (time between end of infusion and injection of radiotracer) of 72.5 ± 51.2 min. After the intravenous administration of 40 mg of citalopram, steady state plasma concentrations and an increase in cortisol and prolactin concentrations were previously observed in both young controls and midlife depressed patients during the same time interval as used in the present study [14,31]. Assays for citalopram and neuroendocrine (cortisol and prolactin) concentrations, taken at predetermined intervals (baseline, end of infusion, 15, 30, 60, 90 and 120 min post-infusion), were performed at the Geriatric Psychopharmacology Laboratory, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, as described previously [8,31].

2.4. PET imaging procedures

The infusions of placebo (250 ml of Saline-Day 1) or citalopram (40 mg of the drug diluted in 250 ml Saline-Day 2) were performed over 60 min. The study was single blind in that the subjects were told that they would receive either placebo (saline) or citalopram prior to each study. The order of placebo-drug administration was not randomized since performing the scan involving citalopram administration first may result in carry over effects of the drug to the second (placebo) scan. In order to avoid such carry over effects, a time interval of three weeks was suggested to be necessary between placebo and drug conditions [14]. The PET scans were performed using a GE Advance Tomograph at North Shore University Hospital, as described previously [31]. Upon the subject’s arrival at the laboratory, one catheter was placed in a vein in the left arm for radiotracer and placebo/citalopram infusion and a second catheter was placed in a vein in the right arm for sampling of citalopram, and neuroendocrine levels.

After the pre-treatment interval, 5 mCi of $^{18}$F-2-deoxy-2-fluoro-D-glucose ($^{18}$F-FDG) was injected as an intravenous bolus. A ten minute transmission scan and a five minute two-dimensional emission scan were acquired prior to the three-dimensional emission scan for photon attenuation correction [4]. The three-dimensional emission scan began at 35 min after injection of the radiotracer and lasted for 10 min. At the end of the PET scan, the subjects were removed from the scanner, and the intravenous lines were removed after completion of the blood sampling. The
Negative correlations with age were also performed between age and the differences in cerebral glucose metabolism from baseline following citalopram administration (on a pixel by pixel basis) were performed using the SPM statistical option: Multi Subjects: conditions and co-variates. Correlations were performed between the pre-treatment intervals (described in Section 2.3) and the regional differences in cerebral glucose metabolism to determine the potential contribution of time dependent effects to the cerebral metabolic alterations.

2.5. Data and image analysis

The procedures for data and image analysis have been described previously [31,33]. Glucose metabolic rates were calculated on a pixel by pixel basis [33]. Image and data processing was performed using the statistical parametric mapping program (SPM99) [10]. The PET scans for each subject were aligned and non-linearly warped into Talairach space, and the images were smoothed with an isotropic Gaussian kernel (FWHM 8 mm for all directions). All of the PET scans (both within and between subjects) were proportionally scaled to a global mean. The correlations between age and the changes in cerebral glucose metabolism from baseline following citalopram administration (on a pixel by pixel basis) were performed using the SPM statistical option: Multi Subjects: conditions and co-variates. Main effect of age was investigated using the contrast (Post-scan: 0, Pre-scan: 0, Age: 1) to identify areas negatively associated with metabolic change. Correlations were also performed between age and the differences in the neuroendocrine (prolactin and cortisol) concentrations after citalopram administration. Correlations were performed between the pre-treatment intervals (described in Section 2.3) and the regional differences in cerebral glucose metabolism to determine the potential contribution of time dependent effects to the cerebral metabolic alterations.

3. Results

The mean plasma concentrations of prolactin and cortisol obtained prior to and following citalopram administration for the total subject sample are reported in Table 1. As observed previously, neuroendocrine concentrations (cortisol and prolactin) demonstrated significant, time-dependent increases from the end of the infusion up to 30 min post-end of infusion. As shown in Table 2, increases in the cortisol levels at the end of infusion and 15 min post-end of infusion were negatively correlated with age ($r = -0.50$ and $0.54$, respectively, $P < 0.05$).

To address the potential impact of age on citalopram bioavailability, correlations were performed between the plasma levels of citalopram at the end of infusion, 15, 30, 60, 90, and 120 min post-end of infusion and age. There were no significant correlations between plasma citalopram levels and age at any of the time points (data not shown).

Table 1
<table>
<thead>
<tr>
<th>Plasma concentrations of prolactin and cortisol after citalopram administration (40 mg, IV)</th>
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<tbody>
<tr>
<td>Pre-infusion</td>
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<tr>
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<tr>
<td>End of infusion (EOI)</td>
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<tr>
<td>15 min post-EOI</td>
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<tr>
<td>30 min post-EOI</td>
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<tr>
<td>60 min post-EOI</td>
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<td>90 min post-EOI</td>
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<td>120 min post-EOI</td>
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Significantly different from baseline * ($P < 0.05$), ** ($P < 0.01$), *** ($P < 0.001$).

Table 2
<table>
<thead>
<tr>
<th>Relationship between normal aging and the change in the plasma concentrations of cortisol and prolactin from baseline following citalopram administration (40 mg, IV)</th>
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<tbody>
<tr>
<td>CORTICOL (ng/ml)</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Baseline</td>
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<tr>
<td>End of infusion (EOI)</td>
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<tr>
<td>15 min post-EOI</td>
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<td>30 min post-EOI</td>
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<td>90 min post-EOI</td>
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<td>120 min post-EOI</td>
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*Significantly different from baseline $P < 0.05$.

Table 3
<table>
<thead>
<tr>
<th>Changes in cerebral glucose metabolism after citalopram administration (40 mg, IV)</th>
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<tbody>
<tr>
<td>Talairach coordinates (x, y, z, mm)</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Positive correlations with age</td>
</tr>
<tr>
<td>10, –72, 36</td>
</tr>
<tr>
<td>16, –36, 48</td>
</tr>
<tr>
<td>4, –68, 28</td>
</tr>
<tr>
<td>–44, –68, 20</td>
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<tr>
<td>Negative correlations with age</td>
</tr>
<tr>
<td>–10, 66, –2</td>
</tr>
<tr>
<td>50, 52, 0</td>
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<tr>
<td>54, 46, –6</td>
</tr>
<tr>
<td>32, 22, 2</td>
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<tr>
<td>56, –34, 28</td>
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<tr>
<td>38, –42, 38</td>
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</tbody>
</table>
$P > 0.05$ for all comparisons). A visual analog scale for the items “happy”, “depressed” and “anxious” administered before and after the placebo/citalopram infusions did not reveal significant changes in mood (data not shown).

Correlations between the change in cerebral glucose metabolism after citalopram administration and age are shown in Table 3 (the Talairach Atlas coordinates, region names, $z$-scores, and cluster sizes are listed). The effects reported were significant at $P \leq 0.001$ (two-tailed, uncorrected for multiple independent comparisons) based upon a priori hypothesized regions from the previous study [31].

After citalopram administration, change in cerebral glucose metabolism in the right precuneus ($10, -72, 36$), $r^2 = 0.6913$, $P \leq 0.001$.

After citalopram administration, change in cerebral glucose metabolism in the left anterior cingulate gyrus ($-10, 46, -2$), $r^2 = 0.6406$, $P \leq 0.001$. 
metabolism was positively correlated with age in the right 
precuneus (BA 7 and 31), right paracentral lobule, and left 
middle temporal gyrus. The correlation for the precuneus 
(BA 7) is shown in Fig. 1. Change in cerebral glucose 
metabolism was negatively correlated with age in the left 
 anterior cingulate gyrus, right inferior and middle frontal 
gyr, right insula, and right inferior parietal lobule (BA 40).
The correlation for the left anterior cingulate gyrus is shown 
in Fig. 2. The pre-treatment interval did not correlate sig-
ificantly with the change in metabolism in these regions.
Correlations were also performed to determine the po-
tential relationship between age and resting metabolism 
to determine age-related differences prior to drug inter-
vention (data not shown). Resting metabolism in the left 
and right middle frontal gyri were negatively correlated 
with age; however, the probability value, \( P < 0.05 \), was 
below the more stringent value, \( P \geq 0.001 \), used for 
the other comparisons. Therefore, the regions in which 
citalopram-induced metabolic changes were correlated 
with age (except the right middle frontal gyrus for which the probability value was below the threshold set for the study) 
did not show age-related differences in the resting state.

4. Discussion

The results of the present study demonstrate a negative 
correlation between age and both baseline cortisol levels 
and the change in cortisol levels after citalopram administra-
tion. This indicates that the cortisol response to an increase 
in serotonin concentrations decreases with normal aging.
Most studies have shown that agents that increase serotonin 
concentrations or act as serotonin receptor agonists increase 
cortisol and prolactin secretion [5]. Few studies have evalu-
ear the neuroendocrine response to serotonin increase in 
normal aging. Based upon the evidence of serotonin modu-
lation of the hypothalamic-pituitary axis (HPA), the effect 
of citalopram administration on cortisol and prolactin se-
cretion may occur through several, non-mutually exclusive 
mechanisms. The citalopram-induced increase in serotonin 
may result in an increase in cortisol levels either due to an 
increase in corticotrophin-releasing factor (CRF) con-
centrations, potentiation of adrenocorticotropic hormone 
(ACTH) release from the anterior pituitary or the release 
of cortisol from the adrenal glands [5]. As CRF or ACTH 
levels were not measured in the current study, the spe-
cific mechanisms underlying the cortisol effects cannot be 
specified. As stated earlier, baseline values of cortisol were 
negatively correlated with age. Citalopram increased both 
cortisol and prolactin, however, a negative correlation with 
age was observed with cortisol only. These findings sug-
gest that basal cortisol levels decline with the normal aging 
process. The change in plasma cortisol levels from baseline 
consistent with decreased serotonergic responsivity in 
normal aging resulting in decreased HPA axis stimulation 
after administration of a serotonin agonist. It is not clear if 
such findings are specific to the serotonin system or would 
be observed after pharmacologic manipulations of other 
neurotransmitter systems (e.g., dopamine, acetylcholine).

The lack of mood changes following citalopram admin-
istration is not surprising given that the subjects enrolled in 
the study were carefully screened for psychiatric disorders, 
particularly affective disorders.

Regarding the neuroimaging data, both positive and neg-
ative correlations with normal aging were observed. The 
positive correlations were observed in posterior cortical 
regions, whereas the negative correlations were observed 
largely in anterior cortical regions (Fig. 3). The major-
ity of the brain regions in which significant correlations 
were observed have shown reductions in metabolism in 
young subjects [31]. Predominantly anterior cortical re-
gions (e.g., sub-regions of the anterior cingulate and frontal 
cortices) show greater reductions with normal aging. We 
have demonstrated recently that patients with geriatric de-
pression show a blunted metabolic response to citalopram 
administration in the right frontal cortex [30]. These find-
ings may suggest that decreases in right frontal metabolism 
in response to citalopram administration reflect an under-
lying compensatory process that enables the individual to 
remain euthymic in response to the increased psychosocial 
and medical stressors that occur in late life, despite the 
neurochemical changes associated with normal aging.

Our finding of negative age-related correlations in largely 
anticipatory cortical regions and positive age-related correlations 
in posterior regions is consistent with the results of previous 
imaging studies. PET studies of regional cerebral glucose 
metabolism found decreasing regional metabolism with in-
creasing age in frontal areas and the anterior cingulate gyrus 
[24, 37, 39]. Significant positive correlations between age and 
metabolism have been found in the cerebellum, thalamus, 
and occipital areas [39]. It is important to note that these 
findings have been observed in the resting state (pharmacologically induced 
serotonin increase).

These alterations in metabolic response with aging should 
be interpreted within the context of age-related changes in 
serotonin innervation. Neuroimaging and post-mortem stud-
ies of the serotonin transporter and receptors, in addition to 
neuroendocrine challenge studies, suggest a decline in the 
functional integrity of the serotonin system with age. PET 

studies have shown age-related declines (approximately 10% 
per decade) in cortical 5-HT\(_{1A}\) receptor availability [18]. 
Post-mortem examinations of 5-HT\(_{1A}\) receptors demonstrate 
mixed results. An age-related decline in prefrontal 5-HT\(_{1A}\) 
binding was reported in both normal controls and individu-
als who committed suicide [1]. Another study observed an 
association between prefrontal cortical binding and age in 
suicides (but not controls) and no effect in other brain re-
gions [16]. Age-related reductions in cortical and hippocam-
pal 5-HT\(_{1A}\) receptor binding have been consistently reported 
in neuroimaging studies in both non-human primates and 

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human subjects [2,12,20,38]. Decreases in cortical 5-HT$_{2A}$ binding of $42 \pm 7\%$ and $57.0 \pm 7.2\%$ have been reported over an age range of 40 and 58 years, respectively [2,20]. Post-mortem studies have shown decreases in the number of 5-HT$_{2A}$ binding sites in frontal and occipital cortices as well as the hippocampus [2,19].

Age-related alterations in serotonin transporter binding are especially relevant to the present study since the serotonin transporter is the initial binding site of the SSRIs, including citalopram. Human neuroimaging studies have consistently shown decreased serotonin transporter binding in the striatum, thalamus, and brainstem (including the raphe) [15,25,35]. Single photon emission computed tomography (SPECT) studies have reported a 6.6% reduction per decade in the striatum [25] and 3.2–4.5% in the midbrain [25,35]; a recent PET study reported reductions of 9.6% in the thalamus and 10.5% in the midbrain per decade [40]. Differences in resolution may account for the relatively greater reductions in midbrain binding in the PET study compared to the SPECT study. Due to the relatively low concentrations of serotonin transporter in the cortex, it is difficult to quantify cortical serotonin transporter binding in vivo. Therefore, the administration of citalopram combined with measurements of cerebral metabolism provides a unique opportunity to evaluate serotonin responsiveness and cortical serotonin transporter function. In contrast to the neuroimaging studies, post-mortem studies have not demonstrated an age-related decline in serotonin transporter binding in the prefrontal cortex or the sub-nuclei of the dorsal raphe nucleus [1,32].

As discussed in an earlier publication [31], the regional pattern of metabolic alterations after citalopram administration is not entirely explained by the regional distribution of the serotonin transporter and may be due to effects of citalopram on other neurotransmitter or second messenger systems [6,28]. The alterations in metabolism are observed primarily in the cortical association areas, whereas the serotonin transporter is located in highest concentrations in sub-cortical regions (e.g. thalamus, striatum) and to a lesser extent throughout the cortex [13]. Given the pattern of metabolic alterations, the relative distribution of glutamate receptors and glutamate concentrations in the cortex, and the evidence suggesting interactions between glutamate and serotonin [31], the alterations in cerebral glucose metabolism may represent secondary effects of increased serotonin concentrations on glutamate neurotransmission. The limited literature regarding the effects of normal aging on the glutamate system report mixed results [27,36]. Further research into the effects of normal aging on the glutamate system and glutamate-serotonin interactions may enhance the interpretation of the cerebral metabolic data. Thus, the findings of alterations in the cortical metabolic response with the normal aging process may reflect functional compensation for the loss of serotonin innervation to these regions.

The results of the present study provide evidence for age-related changes in serotonin responsiveness by using the most direct method currently available to measure serotonin function. The findings of alterations in the cortical metabolic response with the normal aging process may reflect functional compensation for the loss of serotonin innervation to these regions. Future studies will apply this method to evaluate serotonergic dysfunction in late-life neuropsychiatric disorders, including geriatric depression and Alzheimer’s disease.
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