Differences between males and females in rates of serotonin synthesis in human brain
(trypthphan depletion/major depression/α-methyl-l-tryptophan/positron emission tomography imaging)

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ABSTRACT Rates of serotonin synthesis were measured in the human brain using positron emission tomography. The sensitivity of the method is indicated by the fact that measurements are possible even after a substantial lowering of synthesis induced by acute tryptophan depletion. Unlike serotonin levels in human brain, which vary greatly in different brain areas, rates of synthesis of the indolamine are rather uniform throughout the brain. The mean rate of synthesis in normal males was found to be 52% higher than in normal females; this marked difference may be a factor relevant to the lower incidence of major unipolar depression in males.

Low brain serotonin (5-HT) levels or function have been implicated in various types of psychopathology, including depression, suicide, aggression, anxiety, and bulimia (for reviews see refs. 1–3). Until recently, the principal methods for studying serotonin metabolism in human brain were determination of the metabolite of serotonin 5-hydroxyindole-3-acetic acid (5-HIAA) in cerebrospinal fluid (CSF) and postmortem measurements of brain serotonin and 5-HIAA. Both methods have limitations. In particular, neither provides a direct measure of serotonin synthesis in the living brain. Recently, a method for measuring serotonin synthesis in the brain of living mammals has been developed (4–5) and tested successfully in dogs (6). The method uses positron emission tomography (PET) and α-[11C]methyl-L-tryptophan as a tracer. The tracer is converted in part to α-[11C]methylserotonin, which accumulates in serotonin neurons, because it is not a substrate for monoamine oxidase and does not cross the blood–brain barrier.

We report here in vivo measurements of serotonin synthesis in the brain of healthy volunteers. Both male and female subjects were studied because CSF studies suggest that the rate of brain serotonin metabolism is higher in females than in males (7–8), and because the incidence of major unipolar depression is higher in women (9). We measured rates of serotonin synthesis under two conditions: at baseline and after acute tryptophan depletion (ATD). For ATD, subjects ingest a tryptophan-free mixture of all the essential amino acids. This induces protein synthesis, which incorporates body stores of tryptophan-freemixtureofalltheessentialaminoacids.Thisacutetryptophandepletion (ATD). For ATD, subjects ingest a tryptophan-free mixture of all the essential amino acids. This induces protein synthesis, which incorporates body stores of tryptophan, because it is not a substrate for monoamine oxidase and does not cross the blood–brain barrier.

METHODS

Selection of Subjects. Eight male and seven female subjects, aged from 18 to 35 years old, were recruited through newspaper advertisements. Inclusion criteria for all subjects included willingness to participate, good physical and mental health, and a knowledge of the psychiatric health of their first-degree relatives. Exclusion criteria included evidence of a past or present axis-I or axis-II DSM-III-R (Diagnostic Statistical Manual) diagnosis in the subject or first-degree relatives, and any significant medical illness. Psychiatric evaluations were conducted using the Structured Clinical Interview for DSM-III-R, nonpatient version (16). All subjects who participated in the study gave written informed consent. The study was approved by the Research and Ethics Committee of the Montreal Neurological Institute and Hospital and the Ethics Committee of McGill University.

Overview. On the test day, the subject arrived at 7 a.m. for a PET scan of the head, after which mood was rated (see below), a venous blood sample taken, and a PET scan performed. The subjects then ingested a tryptophan-deficient amino acid mixture (see below). Five hours later, mood was reevaluated, and a second PET scan performed.

ATD. ATD was performed as described previously (14). The day before the test day, subjects ingested a low-protein diet. Prepacked, precooked meals, delivered to the subject’s home, contained 160 mg/24 h of tryptophan, 22.6 g/24 h protein, and 2,212 kcal/24 h. Subjects were instructed to eat at regular hours and were allowed ad libitum water and up to 3 cups of coffee or tea per day. On the test day the subject arrived, having fasted since the previous evening. After the first PET scan, the subject ingested a tryptophan-free amino acid mixture, containing 100 g of amino acids, consisting of 15 amino acids in 200 ml, as used by Young et al. (17). The amino acids mixture consisted of L-alanine 5.5 g, L-arginine 4.9 g, L-cysteine 2.7 g, glycine 3.2 g, L-histidine 3.2 g, L-isoleucine 8 g, L-leucine 2.7 g, glycine 3.2 g, L-histidine 3.2 g, L-isoleucine 8 g, L-leucine 2.7 g.

Abbreviations: CSF, cerebrospinal fluid; 5-HIAA, 5-hydroxyindole-3-acetic acid; PET, positron emission tomography; ATD, acute tryptophan depletion; LC, lumped constant; DV, distribution volume.

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The venous input function is normalized to the exposure to calculate a correction factor that was used to normalize the two input functions. The set of both input functions coincided from this experiment, we were able to mine the two input functions. These two input functions were sampled venous and arterial blood simultaneously to determine the arterial input function in the calculation of the venous input function. The plasma free tryptophan was measured in the ultrafiltrate of plasma (10,000 molecular weight cut-off; centrifuged for 5 min at 8,000 × g at 4°C). PET and MRI images were coregistered and superimposed to help in the delineation of the brain structures on PET images (24). The anatomical regions were identified in the MRI, from which outlines were transformed onto PET images. The MRI and PET images were coregistered using a program developed at the McConnell Brain Imaging Center, Montreal Neurological Institute (24). The PET images were acquired by the Scanditronix PC-2048 15B scanner with 6.5-mm intervals between slices. The T1-weighted MRI images of 2-mm thickness were used for the detailed anatomical identification and the coregistration of the PET images. For the coregistration from each dynamic study, two sets of cumulative images were generated. The first set represented a sum of images acquired between 3 and 8 min after tracer injection, and the second set by summing images acquired between 20 and 60 min after tracer injection. The coregistration of the MRI and PET images was carried out by selecting between 15 and 20 anatomical landmarks. Some of the points used for the alignment of images were: the sinus confluence, the junction of the transverse and sigmoid sinuses, a center of the cavernous sinus, anterior tip of the straight sinus (early images), the center of the orbit, the petrous pyramid and frontal sinus, frontal and occipital poles of the brain, the genu of the corpus callosum, the midline of the thalamus, and the base of the frontal and temporal lobes. The tracer concentrations read from these regions were used for further calculations.

The measurements of serotonin synthesis rates are based on the unidirectional trapping of α-methyltryptophan in the brain (4, 6). The method is similar to the deoxyglucose method of Sokoloff et al. (25). We set to emphasize that it has been shown before that this tracer is not incorporated into proteins (4), is not a substrate for tyrosine hydroxylase (26), and there is no appreciable amount of a metabolite present in the plasma, so that the plasma level of radioactivity (M.D. et al., unpublished data), at all times, relates directly to the amount of tracer present. The PET approach used here is based on the serotonin synthesis measurements in the dog brain (6). In short, the tissue unidirectional uptake of tracer (K*; ml g⁻¹·min⁻¹) or the slope of the linear portion (4, 6) of the tracer distribution volume (DV; ml/g) as a function of the exposure time [θ = ∫₀ᵗ C(t)dt/C₀(T); note that θ was normalized as described above] was calculated by the least-squares method. The slopes (K*) were individually calculated for 10 brain structures, in each subject, using the tissue uptake curve between 20 and 60 min (exposure time θ being between approximately 35 and 100 min). The calculation was done on the tissue time–activity curves before (baseline) and after ATD. From the slope K*, the plasma free tryptophan (Cₚ; pmol g⁻¹·min⁻¹) and the in vivo measured lumped constant (LC = 0.42) (5), regional serotonin synthesis rates (R; pmol g⁻¹·min⁻¹) were calculated as R = Cₚ K*/LC (6). The LC is defined in one formulation as the ratio of the ratios of the Michaelis–Menten constants and the tissue volume of distribution for tracer and trace. It can also be defined as the ratio of the tissue uptake of tracer and trace (5). The regional LC was measured in vivo by a direct comparison of the unidirectional tissue uptake of tryptophan and α-methyltryptophan in the rat brain (5). There is no reason to believe that the LC for humans is different from that for rats. However, the LC consists of the ratio of constants for α-methyltryptophan and tryptophan. Thus, it is likely that the ratio does not vary much between different species, nor between different brain regions (5, 25). For example the LC for 2-deoxy-d-glucose in human brain is similar to the one in rat (27). It is not known whether the LC is the same in the subject’s brain before and after ATD. However, rat protein synthesis in the brain does not change when an amino acid is increased, in
contrast to some other organs (e.g., liver; refs. 28, 29). At any rate, if there were a change in the LC, it would probably be the same in males and females rendering sex comparison valid.

The reduction in serotonin synthesis (ratio of values before and after ATD) in the individual subjects was calculated as an antilogarithm of the differences of the log-transformed synthesis rates. Because in the log-transformed data the ratios represent differences between the logarithms, calculation of the SD of the ratio was simplified. The SD of the mean was calculated as the square root of the sum of squares of the relative errors of the individual serotonin synthesis rates. The log transformation of the data yielded normal distribution of data meeting the requirements for the statistical analysis of the ratios. Statistical analysis of all data was done using BMDP statistical programs (BMDP, Los Angeles, 1993).

RESULTS

Examples of the plots of the tissue distribution volume (DV; ml/g) as a function of the exposure time (θ; min) exemplifying the shape of the curve, and the existence of a linear portion suggesting that the biological system achieved an apparent steady state, are shown in Fig. 1 for male (Fig. 1A) and female (Fig. 1B) subjects. In Fig. 1, the curves obtained at baseline (upper curves) and after tryptophan depletion (lower curves) are shown. The analysis of these curves was also carried out by fitting them to the full operation equation (4) in an attempt to compare values of $K^*$ obtained using a sinus corrected venous curve as input function. There was an excellent agreement between values of $K^*$ calculated from the linear portion of the graph and those obtained from the fit to the full-operation equation, indicating further that the biological system came to or close to an apparent steady-state. The latter are requirements for the validity of the use of the approach described by Patlak et al. (30).

Examples of PET images obtained in a male and a female subject are provided in Fig. 2. Regional serotonin synthesis rates are color coded (vertical bar). Serotonin synthesis rates used to construct these pictorial presentations were calculated from the brain radioactivity distribution with certain approximations, because serotonin synthesis rates are related to the slope of the curves, which cannot be visualized in a static image. The images collected between 30 and 60 min after tracer injection were summed to obtain a better visual representation for regional serotonin synthesis rates. Briefly, the brain radioactivity (nCi/g) was converted into DV(T) (ml/g) by dividing it with the plasma tracer concentration [$C_p$ (T)]; nCi/ml). From these plots, the $K^*$ (ml g$^{-1}$ min$^{-1}$), and the apparent volume of the precursor ($V_{app}$, ml/g) were calculated for each brain structure as described for the dog brain before (6). The average value of $V_{app}$ (ml/g) was calculated from the values for the individual brain structures in a particular subject, and this average value of $V_{app}$ was subtracted from the DV images on pixel by pixel bases. DV images were then converted into serotonin synthesis rate images by multiplying them by $C_p$ (plasma free tryptophan; pmol/ml) and dividing them by LC. This conversion is also supported by our recently reported experiments in rat brain (31), where we showed that the $V_{app}$ is almost uniform through the rat brain.

The average rates of serotonin synthesis obtained in male ($n = 7$) and female ($n = 7$) subjects before and after ATD are given in Table 1. These rates at baseline were about 75 and 50 pmol g$^{-1}$ min$^{-1}$ in males and females, respectively (Table 1). After the ATD the rates of synthesis were about 9.5 and 1.5 pmol g$^{-1}$ min$^{-1}$ in males and females, respectively. The rate of serotonin synthesis was reduced by ATD by a factor of about 9.5 in males and of about 40 in females. One male was excluded from these calculations on the basis of the $\chi^2$ statistic, ($P < 0.001$), indicating that he was an outlier. The rates in this subject were rather high and although they would not affect the mean of the male subjects significantly, they would substantially increase the SDs. However, the inclusion of this subject’s values did not change the main effects observed.

The rates of serotonin synthesis (Table 1) were rather uniform throughout the terminal fields of serotonergic neurons of the human brain, as is the case in the rat brain (5). The resolution of our scanner did not permit determination of serotonin synthesis rates in the serotonergic cell body areas of the brain stem.

Male subjects had higher levels of plasma free tryptophan than female subjects (Table 2), but there was no significant correlation between plasma free or total tryptophan levels and rates of serotonin synthesis in either group of subjects (Tables 1 and 2). There was no significant difference in total plasma tryptophan in male and female subjects either at baseline or after ATD (Table 2). The use of the ratios of free or total plasma tryptophan to the plasma levels of other large neutral amino acids as covariates in the ANOVA analysis did not affect the degree of significance of differences between serotonin synthesis rates in male and female subjects. ATD induced a significant reduction ($P < 0.05$ for the sex–time interaction; two-way repeated measures ANOVA on the log transformed data) of serotonin synthesis, as indicated by the ratios of synthesis rates before and after ATD. ATD did not have a statistically significant ($P > 0.05$; two-tailed paired $t$ test) effect on mood ratings overall, though one of seven female subjects (but none of the male subjects) showed signs of distress, low mood, and a crying spell by the end of the second scan.

DISCUSSION

Until recently, the principal method for estimating the rate of serotonin metabolism in the human central nervous system has been the measurement of 5-HIAA in CSF. However, such measurements in lumbar CSF may reflect, in part, spinal cord metabolism of serotonin, and also can be influenced by factors such as the transport of 5-HIAA into and out of the CSF, mixing of CSF, as well as the rate of serotonin catabolism (32). Thus, CSF 5-HIAA level is a poor index of dynamic changes in serotonin
synthesis in brain tissue. The advantages of the PET method are substantial: (i) it measures serotonin synthesis directly in various brain regions; (ii) it can be repeated after a short time interval; (iii) it is less invasive than a lumbar puncture; and (iv) the results are not influenced by a wide variety of factors unrelated to the rate of serotonin synthesis that can alter CSF values. Our method, like other PET methods, involves certain assumptions, as detailed in previous papers (4, 6). The main disadvantages of our method are cost and availability.

The mean rates of serotonin synthesis determined in the present study range from 66 to 85 pmol g\(^{-1}\) min\(^{-1}\) for different brain areas in male subjects and 47 to 55 pmol g\(^{-1}\) min\(^{-1}\) in female subjects. A surprising uniformity in the different areas studied, contrasting with the variable serotonin levels measured in different areas of postmortem brains. For instance, the ratio of serotonin levels in a region with high content, such as caudate, to an area with a low content, such as frontal cortex, is of about 15 (33, 34). In the present study, the ratio for the rate of synthesis in these two areas was 0.9 for male and 1.0 for female subjects. The density of serotonergic innervation of different areas can be estimated by measuring the number of serotonin uptake sites. In postmortem studies on the density of re-uptake sites measured by the binding \(^3\)H-labeled imipramine, cyanoimipramine, or paroxetine in human brain, ratios of the number of binding sites in the caudate to that in the frontal cortex were in the range between 1.2 and 3.3 (35–38). This suggests that the serotonergic innervation of the frontal cortex is less dense than that of the caudate. However, this difference is substantially less than that of serotonin levels. The uniformity observed in the present study in different brain areas suggests that the rate of serotonin synthesis depends on factors other than the density of innervation. Using the postmortem concentrations of serotonin reported by Young et al. (34) for the putamen (466 ng/g) and temporal cortex (11 ng/g), and the present data for the rates of serotonin synthesis, the time required to synthesize an amount of serotonin equal to the tissue content is 31 and 48 min for the putamen of males and females, respectively, and 0.8 and 1.3 min, respectively for the temporal cortex. Thus, for yet unidentified reasons, the storage of serotonin is very much less, in relation to its rate of synthesis, in cortex than in basal ganglia. One could speculate that this seemingly redundant capacity to synthesize serotonin in cortical areas could be related to the ability of the serotonergic system to provide rapidly enough of its neurotransmitter in situations where increased availability is required.

The marked difference in the rates of serotonin synthesis between male and female subjects is, to our knowledge, a new finding. In the few postmortem studies where male-female differences in the brain serotonin levels were examined, no significant differences were found (38, 39). Moreover, no differences have been found between the number of serotonin re-uptake sites in the brains of male and female subjects (35, 39). However, two CSF studies have suggested a higher rate of serotonin synthesis in female than male subjects (7, 8), opposite to the results of the present study. One possible explanation for this apparent discrepancy could be that the system transporting 5-HIAA out of CSF is less active in female than male subjects.
The rate of serotonin synthesis will depend on numerous factors including the free plasma tryptophan levels, the plasma levels of tryptophan relative to the other large neutral amino acids, the activity of the system that transports the large neutral amino acids into brain, the gene expression of tryptophan hydroxylase, degradation of tryptophan hydroxylase, compartmentalization of tryptophan and tryptophan hydroxylase in brain cells, as well as probably numerous other factors. Any difference in the level to which plasma CTP is decreased in males and females is in part related to the metabolic differences of their bodies, and as suggested by data presented in this manuscript, possibly could have influence, by rather complex and not yet well understood processes, on the brain biology. If one accepts the biological model derivation, which is based on the plasma input function, then it must be also accepted that the rate of serotonin synthesis must be somehow related to the plasma CTP, but the relationship is not necessarily linear. Indeed, the presented data suggest that despite reduction in the CTP of 10 and 3.5 times in females and males, respectively, the rate of serotonin synthesis was reduced 40 and 10 times in females and males, respectively. From this large difference between reduction in CTP and the serotonin synthesis rate it is obvious that substantially more complex mechanism(s) controlling brain serotonin synthesis is (are) involved here.

Averaging over the different brain areas, the rate of serotonin synthesis is 52% greater in male than in female subjects. This is one of the largest differences between the brains of males and females that is not related to hormone binding sites. The reason for this difference is not clear at this time. Tryptophan is taken up into the brain by a transport system that is common to all the large neutral amino acids. There is competition between the large neutral amino acids for this system, and the plasma ratio of tryptophan to the other large neutral amino acids best explains its brain level, at least in laboratory animals (41). In the present study, using ratios of the plasma level of free tryptophan to the levels of the other large neutral amino acids as a covariant in the ANOVA analysis did not alter the statistical significance of this difference. This suggests that differences in peripheral tryptophan availability do not explain the sex difference in brain serotonin synthesis, unless there is a large component for the entry of tryptophan into human brain that is not affected by the other large neutral amino acids. In rat brain under steady-state conditions, we reported a substantial diffusion component for the blood–brain transfer of tryptophan (42). What evidence there is from human CSF studies suggests that other large neutral amino acids reduce, as in experimental animals, tryptophan uptake into human brain (43–45).

The possible association between serotonin and major depression suggests that the rate of serotonin synthesis in women may be related to the higher incidence of major unipolar depression. Animal data indicate that female rats adapt less readily than male rats to stress in an animal model of depression, and that serotonin may play a role in this difference (46). Human males and females seem to have similar stores of brain serotonin, but, if there were increased utilization of serotonin during stressful situations, a lower rate of synthesis in the

Table 1. Serotonin synthesis rates in male and female subjects before and after tryptophan depletion

| Brain area          | Male subjects | | Female subjects | |
|---------------------|---------------|-----------------|-----------------|
|                     | Synthesis rate, pmol g⁻¹ min⁻¹ | Ratio†‡ | Synthesis rate, pmol g⁻¹ min⁻¹ | |
|                     | Before*       | After          | Ratio†‡         | Before*       | After          |
| Frontal cortex      | 70 ± 19       | 9 ± 6          | 9.2 ± 1.3       | 43 ± 20       | 1.4 ± 1.0      |
| Parietal cortex     | 73 ± 19       | 10 ± 7         | 9.0 ± 1.3       | 44 ± 21       | 1.4 ± 0.9      |
| Temporal cortex     | 74 ± 19       | 10 ± 6         | 8.9 ± 1.4       | 44 ± 21       | 1.5 ± 1.0      |
| Occipital cortex    | 68 ± 15       | 9 ± 6          | 9.3 ± 1.5       | 40 ± 19       | 1.3 ± 0.9      |
| Caudate             | 64 ± 15       | 8 ± 5          | 9.7 ± 1.6       | 42 ± 19       | 1.3 ± 0.7      |
| Putamen             | 80 ± 19       | 9 ± 6          | 10.5 ± 1.7      | 49 ± 22       | 1.3 ± 0.8      |
| Globus              | 68 ± 18       | 8 ± 6          | 10.4 ± 2.9      | 43 ± 20       | 1.2 ± 1.0      |
| Palidus             | 70 ± 19       | 9 ± 6          | 9.1 ± 1.6       | 47 ± 21       | 1.5 ± 0.9      |
| Thalamus            | 63 ± 22       | 8 ± 5          | 7.9 ± 2.8       | 42 ± 22       | 1.3 ± 1.0      |
| Amygdala and hippocampus | 65 ± 14   | 8 ± 5          | 9.8 ± 2.0       | 42 ± 20       | 1.3 ± 0.9      |

Data are presented as the mean ± SD with seven subjects of each sex. All subjects were scanned before and after plasma tryptophan depletion.

†Synthesis rates in male subjects were statistically different (P < 0.05; ANOVA; analysis of variance), at baseline, from those in female subjects.

‡Significant difference (P < 0.05; two-way repeated measure ANOVA) between the degree of reductions (ratios) in male from that in female subjects.

Table 2. Plasma total and free tryptophan in male and female subjects before and after depletion

<table>
<thead>
<tr>
<th>Plasma tryptophan conc., nmol ml⁻¹</th>
<th>Male subjects</th>
<th>Female subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before*</td>
<td>After</td>
</tr>
<tr>
<td>Free†</td>
<td>12 ± 6</td>
<td>3.4 ± 3.0</td>
</tr>
<tr>
<td>Total‡</td>
<td>64 ± 16</td>
<td>11 ± 6</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD with seven subjects of each sex. All subjects were scanned before and after plasma tryptophan depletion.

†The plasma free tryptophan in male subjects was significantly different (P < 0.05; ANOVA) from that in female subjects at the baseline, but not after ATD. There was no significant correlation (P > 0.05; Pearson rank correlation) between plasma free tryptophan levels and rate of serotonin synthesis shown in Table 1.

‡No significant difference (P > 0.05; ANOVA) between plasma total tryptophan levels at the baseline or after ATD in male and female subjects. There was no significant correlation between plasma total tryptophan levels and the serotonin synthesis rates shown in Table 1.
females may not be as efficient in maintaining adequate stores of the neurotransmitter. Thus, in such situations, serotonin levels would decline more in females than in male subjects, possibly increasing vulnerability to depression.

The effect of ATD in the present study (Table 1) shows that (i) the PET method is capable of measuring rates of serotonin synthesis considerably below baseline rates (e.g. before ATD), and is therefore a suitable method for studies of patients with low rates of serotonin synthesis, and (ii) ATD causes a marked lowering of brain serotonin synthesis in all brain regions examined. The magnitude of the effect in the brain was somewhat greater than the decline in free plasma tryptophan. While the effect of ATD on serotonin synthesis was uniform throughout the brain, the effects on serotonin levels (as opposed to serotonin synthesis) are unlikely to be uniform. For instance, in the cortex, the density of innervation varies more, and serotonin levels are rates of serotonin synthesis so similar in different brain areas, the rate of serotonin synthesis in women.

The reason for the greater biochemical effect of ATD in healthy women were more susceptible than healthy men to a lowering of mood after ATD (47). The present results suggest that this might be related to ATD causing a larger decrease in the rate of serotonin synthesis in women.

The results of this study raise a number of questions. First, why are rates of serotonin synthesis so similar in different brain areas, when the density of innervation varies more, and serotonin levels vary even more? Second, what are the causes and implications of the higher rates of serotonin synthesis in male brains? Gender-related differences in serotonin synthesis could be related to early serotonergic events in the brain organization and/or effects of circulating gonadal hormones. A better understanding of these gender differences reported here might be provided by studies of individuals with pathologically altered levels of gonadal hormones. The possible role of serotonin synthesis in susceptibility to depression could be investigated by studying subjects who are at elevated risk for depression and depressed patients presenting with a major depressive episode.

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