Low brain uptake of L-[^{11}C]5-hydroxytryptophan in major depression: a positron emission tomography study on patients and healthy volunteers

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The precursor of serotonin, L-5-hydroxytryptophan (L-5-HTP), was radiolabelled with ^{11}C in the β-position, yielding [β-^{11}C]serotonin after decarboxylation, allowing positron emission tomography studies of L-5-HTP uptake across the blood-brain barrier. We studied 8 healthy volunteers and 6 patients with histories of DSM-III major depression, 2 with repeated examinations after clinically successful treatment. We report a significantly lower uptake of [^{11}C]5-HTP across the blood-brain barrier in depressed patients, irrespective of phase of illness. The findings emphasize that serotonin is involved in depressive pathophysiology and support earlier suggestions that the transport of 5-HTP across the blood-brain barrier is compromised in major depression.

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The monoamine hypotheses for the etiology of affective disorders were formulated on the basis of pharmacological observations on the inhibition of reuptake of serotonin and norepinephrine by tricyclic antidepressant drugs (1–5). Surprisingly, no relationship has been definitely proven between the mood disorder process and impaired monoamine turnover (6). Studies on turnover in plasma and cerebrospinal fluid have probably been overinterpreted as a source of information for central biochemical function. Antidepressants with different biochemical profiles assessed *in vitro* were long thought to act specifically on different central monoamine functions, which should be reflected in typical alterations in cerebrospinal fluid monoamine metabolites. However, the earlier hypotheses evolved into new concepts involving interactions between different monoamine systems (7–10). Moreover, a well-controlled system may well exist centrally although a low turnover of peripheral monoamines can be shown, and vice versa (6).

This methodological uncertainty demands new methods to illuminate the role of brain monoamines in the pathogenesis of affective illness. Access to direct information about the central turnover and functional output of the neurotransmitter serotonin is essential to prove or disprove the many hypotheses of a serotonin dysfunction in affective illness.

Positron emission tomography (PET) using various ^{11}C tracers has emerged in focus for studies on neurotransmission. The precursor for *in vivo* serotonin synthesis, 5-hydroxytryptophan (5-HTP) labelled with ^{11}C in the β position, has now become available to address this demand to directly study precursor uptake mechanisms and presynaptic serotonin synthesis. Quantification of brain dopamine metabolism using ^{11}C-labelled L-DOPA has also been suggested by our group (11).

Long-term changes in brain uptake of 5-HTP in depressed patients and in patients on drug treatment will be of considerable value for a further understanding of the biological mechanism of the disease process. In this study, results are presented from PET studies on brain use of [β-^{11}C]5-HTP in healthy volunteers and in 6 patients with unipolar depression studied during a depressive episode and/or in remission.

Material and methods

Subjects

Eight healthy male volunteers and 6 patients with histories of major depression according to DSM-III (3 women and 3 men) took part in the study after informed consent. The study was approved by the Ethics Committee of the Faculty of Medicine at

Uppsala University and the Isotope Committee of the University Hospital of Uppsala. Volunteers were objectively and subjectively mentally healthy males (physicians and medical students) between 25–43 years of age. Table 1 gives background data with age, sex, and received radioactive dose.

Patient 1. A 42-year-old depressed woman was investigated with [β-^{11}C]5-HTP shortly after admission to the Department of Psychiatry. The DSM-III diagnosis was major depression, melancholic subtype with positive heredity (her brother had lithium-treated unipolar swings). She had been increasingly ill for the past 4 weeks and was completely drug-naive for any antidepressant drug, although she had experienced some 25 depressive episodes during the preceding 15 years. The longest duration of one episode was 9 weeks. Her Hamilton Rating Scale for Depression (HRSD) (12) score was 26. She fulfilled 4 of 8 Research Diagnostic Criteria (RDC) symptoms for major depressive disorder (appetite loss, sleep disturbance–early awakenings, low energy and low interest; she did not experience guilt and had no suicidal thoughts). A 1-mg dexamethasone suppression test (DST) showed suppression with plasma cortisol 40 nmol/l at 1700. She was reinvestigated with PET 5 weeks after the first investigation following a highly successful treatment period with clomipramine 150 mg daily (HRSD score had dropped to 2) and after another 4 months when she had been off drugs for about 8 weeks (still normothymic).

Table 1. Background data on 8 experiments with L-[β-^{11}C]5-HTP on healthy volunteers and 9 experiments on 6 patients with histories of major depression

ID	Sex	Age	Radioacitivity (MBq)
Healthy volunteers			
1	M	25	151
2	M	27	123
3	M	30	132
4	M	43	141
5	M	28	42
6	M	37	40
7	M	39	164
8	M	31	79
Patients			
1a	F	42	97
1b			74
1c			78
2a	M	36	120
2b			149
3	M	44	160
4	M	34	96
5	F	37	66
6	F	43	116

Patient 2. A 36-year old man, also with positive heredity (his father had lithium-responsive unipolar depressive episodes), investigated with [β-^{11}C]5-HTP. The patient had suffered from over 50 depressive episodes since the age of 26, with an earlier longest duration of 20 weeks. He had been ill for 20 weeks at admission and was off antidepressants for 10 d prior to PET. Lithium alone had earlier been ineffective in preventing recurrences. Fatigue was a major complaint. He fulfilled 5 of 8 RDC symptoms (sleep disturbance–hypersomnia, low energy, low interest, concentration difficulties and psychomotor retardation). DSM-III diagnosis was nonmelancholic subtype of unipolar depression. His HRSD score was 19. The 1-mg DST showed nonsuppression with plasma cortisol 210 nmol/l at 1700. The patient was reinvestigated with PET 9 weeks after the first examination, following a treatment course of combination of phenelzine and lithium citrate. The HRSD score had dropped to 6 but fatigue remained a problem.

Patient 3. This was a 44-year-old man without known heredity for mood disorders. While in a unipolar depressive episode, he was investigated with PET and [β-^{11}C]5-HTP. He had been suffering from about 10 depressive episodes from age 29 with a longest duration of 40 weeks. At admission he had been depressed for 5 weeks after an ictal debut. Before that he had been in remission only for some weeks following electroconvulsive therapy (ECT). For about 9 months he had not been treated with any psychoactive drugs but had received an ECT series 4 months prior to investigation. Over the years he had been treated with several antidepressants and lithium, but only ECT had convincingly been effective on 2 occasions–other episodes had seemingly yielded spontaneously. Current episode fulfilled 6 of 8 RDC symptoms (low appetite, low energy, low interest, guilt, impaired concentration and psychomotor retardation). A 10-year-old daughter suffers from intestinal celiacia successfully treated with a gluten-free diet. The patient repeatedly complained of loose stools during depressive episodes. The DSM-III diagnosis was melancholic subtype of unipolar major depression. His HRSD score was 24. The 1-mg DST showed nonsuppression, with plasma cortisol 420 nmol/l at 1700.

Patient 4. This was a 34-year-old man with heredity for unipolar depression both on the paternal and maternal side; mother had committed suicide after a protracted depression. He had his first depression at age 23 and had suffered from 5 episodes with a maximal duration of 20 weeks. He was responsive to tricyclics. At time of investigation he had been off amitriptyline for 6 weeks and had his last depressive

episode 4 months earlier; he was now relapsing and had already 20 points on the HRSD. The DSM-III diagnosis was melancholic subtype of unipolar major depression. No DST was performed.

Patient 5. A 37-year-old woman without distinct heredity for mood disorder. The first depressive episode was at age 15, and she had suffered about 45 primary unipolar mood swings before the present depressive episode, which had lasted 36 weeks at time of investigation. She had been responsive to tricyclics several times and had now passed the worst phase, aided by clomipramine treatment that had been stopped 10 d before the investigation. Her HRSD score was 17. The DSM-III diagnosis was melancholic subtype of unipolar major depression. The 1-mg DST showed nonsuppression with plasma cortisol 179 nmol/l at 1700.

Patient 6. A 43-year-old woman with heredity for alcoholism and personality disorder on the paternal side. She had suffered from 3 distinct melancholic major depressive episodes at late springs during the past 3 years with a longest duration of 30 weeks. She was responsive to tricyclics. At time of investigation she had been in full remission for about 6 months and had been off antidepressant medication for 4 months. Her HRSD rating was 6.

Radiochemistry

The radionuclide ^{11}C was produced by a ^{14}N(p,α) ^{11}C nuclear reaction using the Tandem Accelerator at The Svedberg Laboratory of Uppsala University. ^{11}C was obtained as [^{11}C]carbon dioxide and used in the synthesis of [^{11}C]5-HTP (13). The molecule was labelled in the beta position with ^{11}C. After decarboxylation by L-aromatic amino acid decarboxylase (AADC) this atom forms part of the serotonin molecule. For each production process, the analysis of radiochemical and chemical purity was performed by means of liquid chromatography on the buffer solution of [β-^{11}C]5-HTP, which also was passed through a 0.22-μm filter before being administered intravenously to the patient. The amount of mass and radioactivity administered were within the ranges of 12–45 μg and 40–160 MBq, respectively.

PET procedure

PET was performed with the patient lying and with the head fixed a PC 384-3B tomograph (Scanditronix, Uppsala, Sweden). Calibration of the tomograph was done according to procedures described (14). Imaging started immediately after intravenous administration of the radioactive ligand and lasted for about 40 min. The PET camera in current use produces 3 reconstructed horizontal brain slices. The top-most level 3 was set to include the basal ganglia. Level 2 was 13 mm down. Level 1 was a further 13 mm down in an attempt to reach cerebellar regions. After reconstruction, regions of interest (ROI) were determined with guidance from a CT scan that had been carried out to obtain coordinates for the head fixation device. The following ROI were selected for comparisons: whole brain at levels 2 and 3 (total area of brain slice); prefrontal cortex at levels 2 and 3 (analyzed separately at dorsolateral and medial areas, Brodmann areas 9–10 and 32, respectively); basal ganglia including the lentiform nucleus and the caudate nucleus at level 3; lentiform nucleus (including the putamen and globus pallidus) at level 3 and caudate nucleus at level 3.

Measured uptake of radioactivity was normalized to radioactive dose injected, radioactive decay, and weight of subject and expressed as a dimensionless unit:

$$\frac{\text{tissue radioactivity/cm}^3}{\text{injected radioactivity/g body weight}}$$

Because of the medium resolution of the PET images, measurements on right and left side of the brain were averaged.

Calculations

Uptake members from ROI were transferred to a Macintosh II computer for mathematical treatment by various locally developed procedures in programs such as Excel, Kaleidagraph and StatView II.

We performed a simple kinetic study of relative radioactivity uptake over time. Group differences in uptake values were tested by *t*-tests. Differences between individual patients and pooled controls were judged by investigating whether a patient value fell outside the 95% confidence interval of the volunteers.

Results

Whole brain as well as regional brain uptakes from 10 experiments on 8 healthy volunteers, used to establish normal values (means ± SEM) are summarized in Table 2. Brain uptakes from 5 min post-injection of tracer (upper panel of Table 2) showed fairly narrow variances between healthy volunteers. Average uptake (± SEM) in whole brain at level 2 was 0.882 ± 0.053 min^{-1} with highest average uptake in the lentiform nucleus, 0.910 ± 0.069 min^{-1}. The normal values are contrasted with values of the 6 individual patients (lower panel of Table 2), of which 1 was re-examined twice and 1 once. Baseline radioactivity uptakes of the 6 depressed patients (0.626 ± 0.045 min^{-1}) were lower than in the

Table 2. Normalized uptake of L-[β-^{11}C]5-HTP in the brain. Individual measurements are averaged from 5 min after injection onward

ID	Whole brain	Prefrontal cortex Dorsolateral area		Medial area		Basal ganglia	Caudate nucleus	Lentiform nucleus
	Level 2	Level 2	Level 3	Level 2	Level 3			
Healthy volunteers								
1	0.863	0.880	0.878	0.950	0.845	0.975	0.915	1.013
2	0.872	0.930	0.833	0.923	0.905	0.977	1.006	0.958
3	0.828	0.820	0.802	0.826	0.811	0.905	0.793	0.969
4	1.107	1.046	1.060	1.079	1.014	1.100	0.988	1.166
5	0.808	0.776	0.860	0.939	0.827	0.845	0.898	0.832
6	0.897	0.958	0.935	0.885	1.047	0.588	0.594	0.567
7	1.057	1.072	1.090	1.025	0.984	1.084	1.100	1.063
8	0.624	0.698	0.636	0.675	0.497	0.680	0.659	0.712
Mean	**0.882**	**0.898**	**0.887**	**0.913**	**0.866**	**0.894**	**0.869**	**0.910**
(+1.96 SEM)	0.986	0.988	0.987	0.999	0.987	1.021	0.990	1.046
(−1.96 SEM)	0.778	0.807	0.786	0.827	0.746	0.768	0.748	0.774
Depressed patients								
1a	0.712 ●	0.858	0.720 ●	0.784 ●	0.629 ●	0.757 ●	0.699 ●	0.808 ●
b 5 weeks	0.763 ●	0.781 ●	0.775 ●	0.850	0.690 ●	0.807	0.758	0.844
c 4 months	0.718 ●	0.825	0.707 ●	0.812 ●	0.645 ●	0.752 ●	0.679 ●	0.794
2a	0.684 ●	0.682 ●	0.656 ●	0.652 ●	0.664 ●	0.743 ●	0.670 ●	0.803
b 9 weeks	0.671 ●	0.666 ●	0.656 ●	0.565 ●	0.630 ●	0.743 ●	0.631 ●	0.815
3	0.801	0.865	0.883	0.936	0.775	1.017	0.996 ○	1.049 ○
4	0.565 ●	0.528 ●	0.503 ●	0.526 ●	0.528 ●	0.614 ●	0.593 ●	0.649 ●
5	0.567 ●	0.606 ●	0.568 ●	0.690 ●	0.627 ●	0.644 ●	0.639 ●	0.672 ●
6	0.426 ●	0.402 ●	0.422 ●	0.443 ●	0.410 ●	0.466 ●	0.468 ●	0.650 ●
Mean	**0.626**	**0.657**	**0.625**	**0.672**	**0.606**	**0.707**	**0.678**	**0.772**
	(t = − 3.32)	(t = − 2.88)	(t = − 3.15)	(t = − 3.01)	(t = − 3.11)	(t = − 1.89)	(t = − 2.02)	(t = − 1.42)
(+1.96 SEM)	0.714	0.789	0.754	0.806	0.683	0.846	0.817	0.911
(−1.96 SEM)	0.537	0.525	0.497	0.538	0.528	0.568	0.538	0.632

Means from patients are from baseline experiments only. Symbols ● and ○ mark values outside the 95% confidence intervals of the means from the healthy volunteers (● for negative and ○ for positive deviations). Means of healthy volunteers are compared with means of baseline experiments on patients by two-sample t-tests ($t > 2.18$ is significant at the 5% level with df = 12).

experiments on healthy volunteers in whole brain level 2 (t = 3.68, df = 12, $P < 0.01$). The difference was more pronounced in prefrontal cortical area than in the striatal areas.

Fig. 1 shows graphs of the uptake per exposure over time, averaged over healthy subjects and patients at whole brain and basal ganglia. Whole brain uptake demonstrates a slight increase in radioactive uptake to 20–25 min followed by a slight decrease. The basal ganglia show a steady increase in radioactivity during the entire course of the experiments. Averaging uptakes from 5 min onward after the injection (as in Table 2) created the impression that basal ganglia showed a comparatively smaller reduction of uptake than other measured brain regions. Nonetheless, Fig. 1 clearly shows that after a time lag of about 15 min, there is a distinct difference also in basal ganglia.

Comparing individual patients with the 95% confidence interval of the normal volunteers demonstrated more strongly significant differences: 5 of 6 patients were below this interval in whole brain, prefrontal cortical areas and the caudate nucleus (Table 2). One patient had "normal" uptake values in whole brain and prefrontal cortex but significantly higher uptake in the striatal regions.

The 2 re-examined patients did not demonstrate any normalization of radioactivity uptake. The significantly lower uptakes at the 2–3 re-examinations of patients 1 and 2 were stable and well below the lower limit of the confidence interval of the healthy volunteers. The lowest uptake was observed in the fully remitted patient. The low uptake of L-[β-^{11}C]5-HTP in depressed patients would then represent mainly a trait characteristic. One healthy volunteer (no. 8) had a low uptake in the range of depressed patients; otherwise there was no overlap.

Discussion

Our results indicate a distinctly lower uptake of the serotonin precursor 5-HTP across the blood-brain barrier in depression compared with healthy individuals. Delineation of ROI was essentially non-

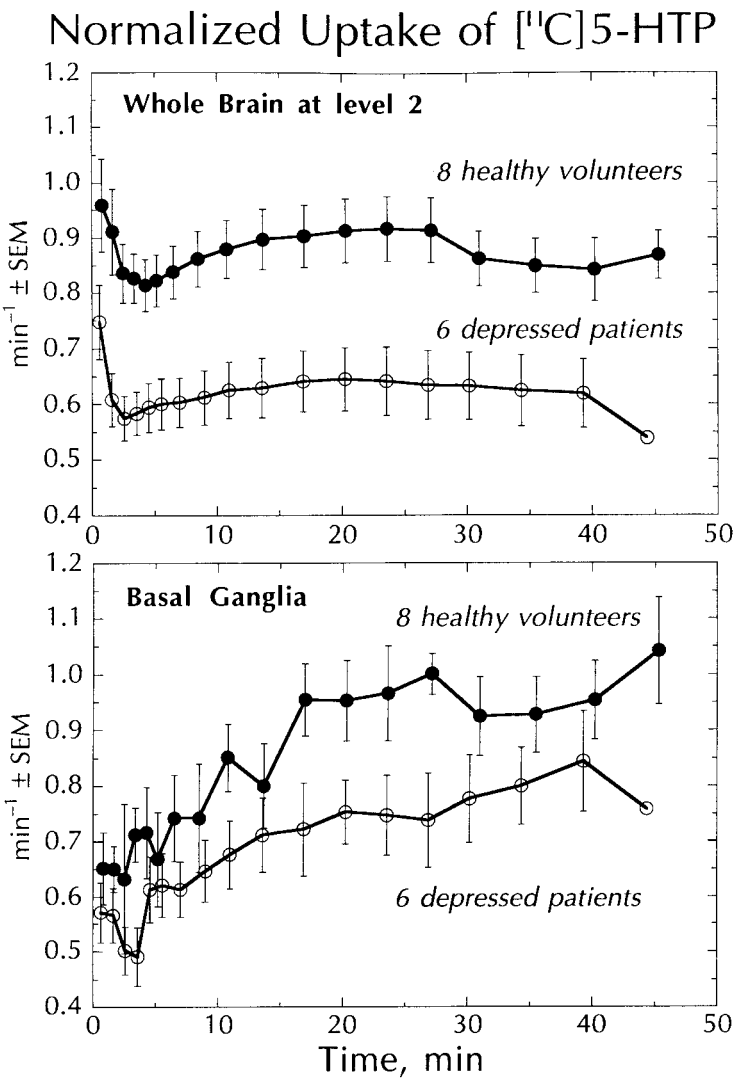

Fig. 1. Uptake of L-[β-^{11}C]5-HTP-derived radioactivity in whole brain and in basal ganglia after intravenous administration of tracer in 8 healthy volunteers and 6 baseline experiments on depressed patients. See Table 2 for individual averages of uptake from 5 min post-injection to end of experiment.

problematic. Special care was taken not to include any ventricular area in any ROI, for instance into the medial prefrontal areas. Such concerns in a number of cases prompted a narrower redelineation, well away from any ventricular space. The results did not change. The spatial resolution of the camera in use with the ^{11}C isotope is about 8 mm. All ROI selected were considerably larger than this limit.

The increasing radioactivities seen in basal ganglia compared with other brain areas (Fig. 1) clearly demonstrate selective use of the radiotracer (11). The quantification of the use rate, i.e. fractional rate of decarboxylation, is cumbersome because of difficulties in finding an adequate reference region. Our efforts to quantify this rate will be published separately.

A generally low uptake of [β-^{11}C]5-HTP both during depressive episodes and after clinical recovery suggests that compromised uptake of 5-HTP plays a role in the diathesis to depression. Obviously, our number of volunteers and patients is still small, but the number of data on each individual nevertheless allows some tentative conclusions.

Serotonin has been thought to act as an inhibitory neurotransmitter in the cerebral cortex (15, 16) but, depending on which receptor is activated, it can also initiate excitation (17). Baxter et al. (18) have provided evidence for a reduction in glucose metabolism in the prefrontal cortex of depressed patients studied by PET using [^{18}F]fluorodeoxyglucose. In schizophrenia, cerebral blood flow studies have indicated dysfunctions elicited by cognitive demands to be localized in the dorsolateral prefrontal cortex and linked to the pathophysiology of a regional specific neural system (19–21). Similarly, animal studies of cortical dopamine metabolism indicate that prefron-

tal cortex is specifically important in the metabolic response to antipsychotic drugs.

A cautionary note on the generally decreased uptake of L-[^{11}C]5-HTP in depression should be added. Any unexpected finding of "too little" or "too much" should warn against interpreting findings in any mechanistic manner. For example, we know from the literature on CSF monoamine metabolites in humans how simple univariate notions of mean levels have evolved into a greater emphasis on interactions between 2 or many neurotransmitter systems and deepened the meaning of variance to grasp concepts such as stability over time.

More than 15 years ago Prange launched the permissive hypothesis in which "low" serotonin would predispose a subject to depression (22), an idea that was supported by van Praag (23). However, simple measurements of regional brain levels of serotonin and 5-HIAA have been measured repeatedly in depressive human postmortem materials, but no unequivocal conclusions have been secured (24–30).

It is important to note that the present PET method at best measures a non-synaptic pool of serotonin metabolism, and is not expected to be informative about synaptic-releasing events. Support for the present findings of low 5-HTP uptake is offered by studies on the concentration of L-tryptophan in plasma. It has long been known that serotonin biosynthesis in brain is regulated by a high affinity uptake of tryptophan into serotonergic neurons (31). Intestinal uptake of L-tryptophan is decreased (32, 33) and the plasma concentration of L-tryptophan is low in depression (34, 35). Recent dietary experiments on normal volunteers are supportive, since a tryptophan-free diet caused a marked depletion of plasma tryptophan by 5 h, at which time the subjects had significantly elevated scores on a depression checklist (36). A tryptophan-impoverished diet has also been reported to cause a rapid relapse in pharmacologically remitted depressives (37).

Psychoendocrine strategies have also contributed indirect evidence linking disturbed serotonin mechanisms to depression. Plasma prolactin response to the centrally acting serotonin-releasing agent fenfluramine is blunted in depression and personality disorders compared with normal controls, irrespective of severity of illness (38, 39). This test was suggested to yield a promising index of "net" or overall central serotonin activity. It is of interest to note that the reduction in serotonin-related events is in the magnitude of 30% both in the recent Coccaro et al. study and in the present PET results. Other challenge tests of serotonergic function have yielded similar results. For example, a recent study by Deakin et al. showed growth hormone response to an intravenous load of L-tryptophan to be attenuated in major depressive patients compared with normal controls, and the prolactin response to the same load to be attenuated in depressives without weight loss (40).

Whether this tentative evidence of a reduction in the presynaptic pool of serotonin in depression and maybe other mental disorders should necessarily translate into a notion of some less efficient serotonergic synaptic signalling system is an issue that obviously cannot be addressed by these studies.

Further investigation should focus on the relationship between the biochemical derangements and more specific depressive issues. Trait *vs* state relationships need further clarification, and we do not know which aspects of mental illness might relate to impaired precursor uptake and which might relate to altered intraneuronal neurotransmitter synthesis. Ongoing studies will address to what extent the putative transport defect is specific for 5-HTP or will hold also for other amino acid precursors for neurotransmitter synthesis, such as L-DOPA, and whether the defect is shared in common between several mental disorders.

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