Serotonin Uptake Sites and Serotonin Receptors Are Altered in the Limbic System of Schizophrenics

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Serotonin (5-HT) uptake sites were mapped by autoradiographic means with [^{3}H]cyano-imipramine ([^{3}H]CN-IMI), the 5-HT$_{1A}$ receptor with [^{3}H]8-hydroxy-2-[di-n-propyl-amino]tetralin ([^{3}H]8-OH-DPAT), and the 5-HT$_2$ receptor with both [^{3}H]ketanserin and [^{125}I]lysergic acid diethylamide ([^{125}I]LSD) in eight nonneurologic controls and 10 cases with a diagnosis of schizophrenia. In the striatum, there was a marked heterogeneous patterning of 5-HT uptake sites that corresponded to the striosomal/matrix compartmentalization of the striatum. This organization was not matched with an equally heterogeneous pattern of either 5-HT$_2$ or 5-HT$_{1A}$ receptors. For the isocortex, a general organizational scheme was observed with the 5-HT$_{1A}$ receptor expression high in the external laminae and deep laminae, but 5-HT$_2$ receptor expression was higher in the internal laminae. There was a laminar distribution of 5-HT uptake sites that approximated the combined distributions of the 5-HT$_{1A}$ receptor and the 5-HT$_2$ receptor. In the parahippocampal gyrus and hippocampus, the distribution of 5-HT uptake sites was complementary to the distribution of 5-HT$_{1A}$ and 5-HT$_2$ receptors. In schizophrenic cases, there was a large increase in the number and altered striosomal/matrix organization of 5-HT uptake sites in the striatum. There was also an increase in the numbers of 5-HT$_2$ receptors in the nucleus accumbens and ventral putamen of the schizophrenics. The number of 5-HT$_{1A}$ receptors was not modified. There was a marked reduction in 5-HT uptake sites in the external and middle laminae of the anterior cingulate, frontal cortex, and posterior cingulate, and no changes were observed in the motor cortex, temporal cortex, or hippocampus. Increased numbers of 5-HT$_{1A}$ receptors were found in the posterior cingulate, motor cortex, and hippocampus. Serotonin$_2$ receptors were substantially elevated in the posterior cingulate, temporal cortex, and hippocampus, but not in the frontal, anterior cingulate, or motor cortices. Examination of the temporal lobe and hippocampus of a group of nonschizophrenic suicides (n = 8) indicated the alterations in 5-HT system in the limbic regions of the striatum, the limbic cortex, and hippocampus of the schizophrenic cases may be disease specific. ***[Neuropsychopharmacology 8:315–336, 1993.***

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Received October 9, 1991; revised June 11, 1992 and October 19, 1992; accepted October 26, 1992.

Published by Elsevier Science Publishing Co., Inc.
655 Avenue of the Americas, New York, NY 10010

KEY WORDS: *Quantitative autoradiography; Serotonin uptake; Serotonin$_{1A}$ receptor; Serotonin$_2$ receptor; Striatum; Cortex; Hippocampus; Schizophrenia*

0893-133X/93/$6.00

Although the role for dopamine (DA) in schizophrenia has received considerable attention, a possible role for serotonin (5-HT) is under investigation (see Bleich et al. 1988; Meltzer 1989). However, the evidence has been largely indirect; investigators have shown that some

antipsychotics have affinity for both DA and 5-HT receptors (Meltzer et al. 1989), or selective (e.g., risperidone, setoperone, and ritanserin) serotonergic properties (Castelão et al. 1989; Vinar et al. 1989). Direct evidence for changes in the levels of 5-HT or density of 5-HT receptors in the brains of schizophrenics has been difficult to obtain. Although some groups have reported changes in levels of 5-HT in the cortex of schizophrenic cases, the only replicable finding has shown increased 5-HT and/or 5-hydroxyindoleacetic acid (5-HIAA) in the putamen and globus pallidus (Crow et al. 1979; Farley et al. 1980; Korpi et al. 1986). However, these findings were not supported by the earlier findings of Joseph and associates (1979) and Winblad and associates (1979), who determined that the most affected region was the hippocampus. Some of the variability in the results of these studies may be related to the fact that a significant number of schizophrenics attempt suicide (Roy 1984) and reduced concentrations of forebrain 5-HT content and numbers of the high-affinity 5-HT transport (uptake) sites have been reported in the brains of suicide victims (Crow et al. 1984; Gross-Isseroff et al. 1989; Stanley et al. 1982).

The physiologic actions of 5-HT appear to be mediated by its interaction with three general classes of receptors: 5-HT_1, 5-HT_2, and 5-HT_3 (for review see, Frazer et al. 1990). The density of 5-HT_2 receptors, labeled with [^{3}H]lysergic acid diethylamide ([^{3}H]LSD) or [^{3}H]ketanserin, has been shown to be reduced (Bennett et al. 1979; Mita et al. 1986), unchanged, or increased (Whitaker et al. 1981; Reynolds et al. 1983) in the frontal cortex of schizophrenic cases. Again, variability in results may be caused by the inclusion of individuals whose death occurred by suicide, as there have been reports of increased densities of 5-HT receptors (Stanley and Mann 1983; Mann et al. 1986; Arango et al. 1990; Arora and Meltzer 1989a) and decreased densities (Crow et al. 1984; Gross-Isseroff et al. 1990) for suicide cases. Recently, Hashimoto and associates (1991) reported an increase in 5-HT_{1A} receptors in the frontal and temporal cortex of schizophrenic cases. However, such changes have also been observed in patients committing suicide (Dillon et al. 1991). Consequently, it is unclear to what extent alterations in the 5-HT system in schizophrenic cases is disease specific.

Receptor autoradiography can be a particularly useful tool for exploring the altered expression of transmitter systems in brains of patients with neuropsychiatric disorders (Joyce et al. 1988, 1992). Studies that directly explore the relationship between the distribution of 5-HT uptake sites and 5-HT receptors in human brain by using autoradiographic means have not been published. Moreover, much of the research on the receptor disturbances in schizophrenia predates the development of radioligands selective for subtypes of the 5-HT receptor, and of radioligands that can selectively label the uptake site for 5-HT located on 5-HT terminals. To determine whether alterations in the 5-HT system can occur in schizophrenic cases, the autoradiographic mapping of 5-HT uptake sites, 5-HT_{1A} and 5-HT_1 receptors sites, was examined in tissue sections obtained from 10 subjects with a diagnosis of schizophrenia and eight cases of nonschizophrenic suicide and compared to those of eight controls. The distribution of high-affinity uptake sites for 5-HT was mapped with the compound [^{3}H]cyano-imipramine ([^{3}H]CN-IMI) (Joyce et al. 1992; Kovachich et al. 1988), the 5-HT_{1A} receptor of the 5-HT_1 family with [^{3}H]8-hydroxy-2-[di-*n*-propyl-amino]tetralin ([^{3}H]8-OH-DPAT) (Pazos et al. 1987a), and 5-HT_2 receptors with both [^{3}H]ketanserin (Pazos et al. 1987b) and [^{125}I]LSD (Engel et al. 1984).

MATERIALS AND METHODS

Human Autopsy Tissue

Whole brain hemispheres were obtained from the Brain Tissue Resource Center of McLean Hospital, Harvard University, Boston, Massachusetts and from the Neuropathology Section, Clinical Brain Disorders Branch of the National Institute of Mental Health, Bethesda, Maryland. Brain tissues were taken from 10 subjects with a diagnosis of schizophrenia and eight cases of nonschizophrenic suicide (Table 1). In all cases the diagnosis of schizophrenia was confirmed by two independent clinicians using DSM-III-R criteria. Determination of drug consumption was based upon retrospective analysis of case reports and toxicology screening. One schizophrenic case had a prefrontal lobotomy and had taken antiseizure medicine. On the basis of interviews with the family or close relatives, the nonschizophrenic suicide cases were identified as not having a history of schizophrenia and a probable history of affective illness. One patient died from suffocation while asleep; high levels of ethanol were subsequently found at autopsy. This patient had a history of manic-depressive illness but was not judged to have committed suicide. The postmortem interval (PMI), determined for all cases as the time between death and initiation of autopsy procedures, varied from 2 to 29 hours.

In all cases where tissue was provided by sources outside the Hospital of the University of Pennsylvania, the tissue was frozen at autopsy and stored at −80°C until processed for autoradiography. Tissue from the two cases with a diagnosis of suicide was obtained from the Medical Examiner's office of the City of Philadelphia (H.M. Mirchandani, Chief Medical Examiner) and the tissue was frozen at autopsy by one of the authors (JNJ). Brain tissue from six age-matched controls was obtained at autopsy (PMI 6 to 24 hours) from the Hos-

Table 1. Data for Autopsy Cases

Case No.	Age	Sex	PMI	Cause of Death	Medication History	Hem	Source
Controls							
1	66 yrs	F	19 hr	cardiac arrest	none (−)	left	HUP
2	84 yrs	M	24 hr	cardiac arrest	none (−)	right	HUP
3	80 yrs	M	21 hr	respiratory arrest	none (−)	left	HUP
4	60 yrs	F	18 hr	cardiac arrest	none (−)	left	HUP
5	77 yrs	M	6 hr	respiratory arrest	ethanol (+)	right	HUP
6	82 yrs	F	19 hr	cardiac arrest	none (−)	left	HUP
7	56 yrs	M	24 hr	respiratory arrest	none (−)	Both	ME
8	40 yrs	F	24 hr	auto accident	none (−)	Both	ME
Means n = 8	68 ± 15	4F,4M	19 ± 6				
Schizophrenia							
9[a]	56 yrs	M	28 hr	cardiac arrest	dilantin, chloralhydrate (+)	Both	NIMH
10	27 yrs	M	8 hr	hanging	proloxin	right	McLean
11	59 yrs	M	24 hr	cardiac arrest	none (−)	left	McLean
12	52 yrs	M	28 hr	cardiomyopathy	haldol	right	NIMH
13	51 yrs	F	12 hr	cardiac arrest	thorazine (+), haldol (−)	left	NIMH
14	82 yrs	M	18 hr	cardiac arrest	haldol, valium, dilantin	Both	HUP
15	65 yrs	M	2 hr	psepsis	none (−)	left	McLean
16	30 yrs	M	3 hr	suicide—drowning	none (−)	right	NIMH
17	36 yrs	F	11 hr	suicide—jumping	none (−)	left	NIMH
18	30 yrs	F	6 hr	suicide—jumping	trilafin (−)	Both	NIMH
Means n = 10	49 ± 18	7M,3F	14 ± 10				
Suicide/Affective Illness							
19	59 yrs	F	25 hr	jumping	imipramine, amytryptilene (+)	right	NIMH
20[b]	49 yrs	F	28 hr	suffocation	ethanol (+)	left	NIMH
21	28 yrs	F	34 hr	gunshot—abdomen	nomifensine (+)	Both	NIMH
22	32 yrs	M	18 hr	gunshot—head	imipramine, benadryl (+)	left	NIMH
23	40 yrs	M	23 hr	gunshot—head	ethanol	right	NIMH
24	39 yrs	M	33 hr	jumping	nardil (+)	right	NIMH
25	15 yrs	M	29 hr	gunshot—head	none (−)	left	ME
26	43 yrs	M	29 hr	gunshot—head	none (−)	right	ME
Means n = 8	38 ± 13	3F,5M	27 ± 9				

In all cases the tissue had been frozen at autopsy and stored at −80°C until processed for autoradiography. Cases were obtained from Hospital of the University of Pennsylvania (HUP), St. Elizabeths Hospital, National Institute of Mental Health (NIMH), McLean Hospital (McLean) or the Medical Examiner's office, City of Philadelphia (ME) as detailed in Materials and Methods. The mean ± standard deviation is given for the age and PMI for the control, schizophrenia, and suicide/affective illness groups.

(+) Indicates positive for drugs with toxicology screen.

(−) Indicates negative for drug with toxicology screen.

[a] Prefrontal lobotomy.

[b] Diagnosis of manic-depressive, suffocation was not a suicide.

pital of the University of Pennsylvania (J. Trojanowski, Director of Medical Pathology), rapidly frozen at −40°C, and stored at −80°C. Two additional control cases were obtained from the Medical Examiner's office of the City of Philadelphia, rapidly frozen at −40°C, and stored at −80°C. The control group was composed of individuals who died of natural or accidental causes and had no history of neurologic or psychiatric disease. Gross pathology of the control brains at autopsy appeared normal. There were no significant differences in the mean age or PMI between the controls, schizophrenic cases, or nonschizophrenic suicide cases.

For the control and schizophrenic cases, coronal slabs at three anterior–posterior levels of the brain were sectioned and processed for receptor autoradiography. The anterior section (Fig. 1A) included the head of the caudate, rostral putamen, anterior cingulate (area 24), premotor (area 6), and frontal cortex (area 9, not including frontal pole). The midcoronal level contained the caudate, putamen, globus pallidus, and frontal cortex (Fig. 1B). The posterior level included the precentral cortex (areas 4 and 23), postcentral cortex (areas 1 and 5), temporal cortex (Brodmann's 22, 41, 42 and 20, 21, 37, not including rostral pole), posterior cingulate, parahippocampus, and hippocampus (Fig. 1C). In all control and schizophrenic cases, the coronal levels were matched for rostral–caudal position. For the suicide cases, coronal levels containing the hippocampus with the temporal and parietal cortex solely were used. For autoradiographic experiments, the brains were sectioned at 20 μm in a Lipshaw 1800-N cryotome at −25°C, thaw-mounted onto gelatin-subbed slides,

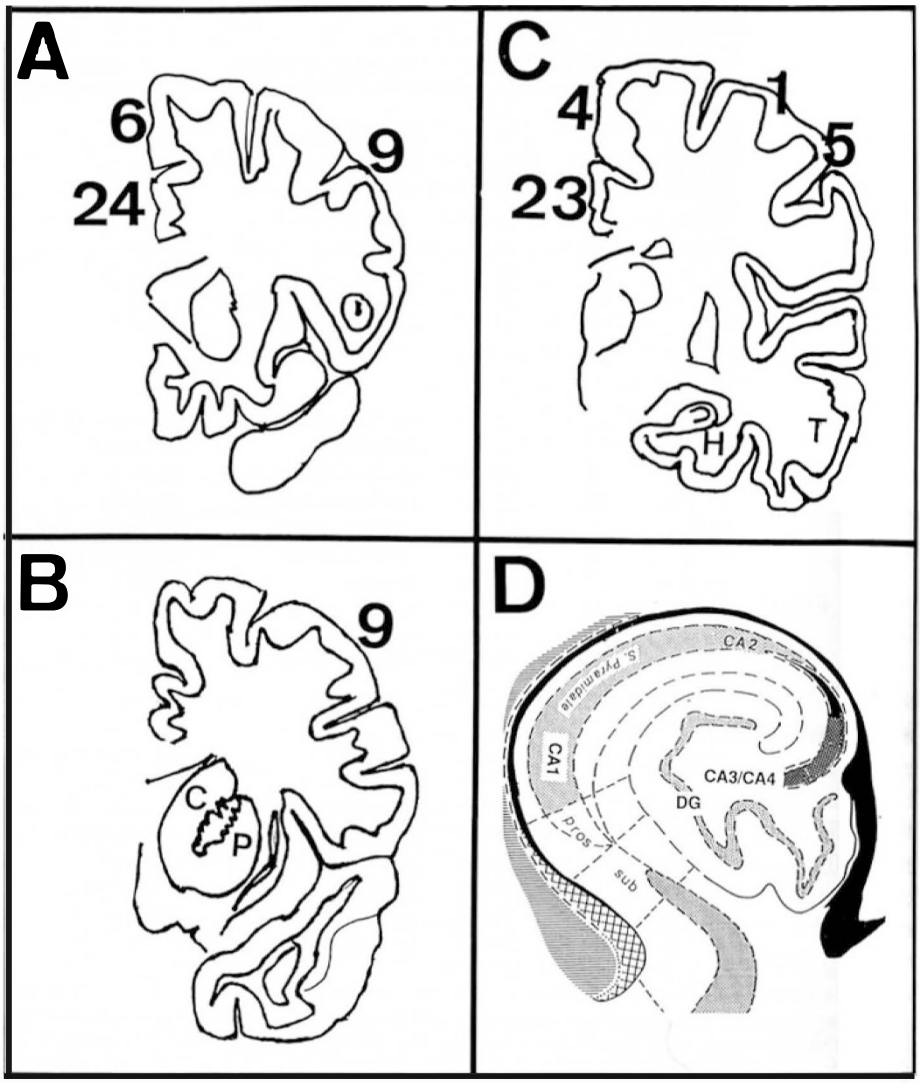

Figure 1. Schematic diagram showing regions analyzed by each level (A, B, C) and the subfields of the hippocampus (D). Abbreviations: area 6, premotor; area 24, anterior cingulate; area 9, prefrontal; area 4, motor cortex; area 23, cingulate cortex; areas 1 and 5, somatosensory; C, caudate nucleus; CA_1–CA_4, subfields of the hippocampus; H, parahippocampus and hippocampus; P, putamen; T, temporal cortex.

dried at 0°C under reduced pressure, and stored at −80°C until further use in the experiments. Every 20th section was retained for Nissl staining.

Radioligand Protocols

Two radioligands were utilized to label 5-HT_2 receptors in tissue sections. The protocol for [^{3}H]ketanserin labeling of 5-HT_2 receptors was adapted from that of Pazos and associates (1987b) and the procedure for [^{125}I]LSD labeling of 5-HT_2 receptors was modified from that of Engel and associates (1984). Information from the use of both radioligands was utilized to address issues of the specificity for [^{125}I]LSD labeling of 5-HT_2 receptors. Tissue sections were preincubated for 15 minutes at room temperature in the incubation buffer. Sections were incubated with 2 nmol/L [^{3}H]ketanserin (61 Ci/mmol; DuPont New England Nuclear) in a buffer containing 0.17 mol/L Tris, pH 7.7, for 2 hours at room temperature. Adjacent sections were incubated similarly but contained 1 µmol/L mianserin for the definition of nonspecific binding. Slide-mounted sections were washed two times for 5 minutes each at 4°C and briefly rinsed in H_2O before drying. Alternating sets of slide-mounted tissue sections were incubated with 200 pmol/L (or in some regions 200 pmol/L, 700 pmol/L, 900 pmol/L, 1.1 nmol/L, and 1.9 nmol/L) [^{125}I]LSD (2200 Ci/mmol; DuPont New England Nuclear) in a buffer containing 50 mmol/L Tris pH 7.4, 10 µmol/L sulpiride, 1 µmol/L tripolidine, and 1 µmol/L prazosin. Adjacent sections were incubated similarly but contained 1 µmol/L ketanserin for the definition of nonspecific binding. The results of preliminary experiments done to define optimal incubation procedures, in which the binding of 200 pmol/L [^{125}I]LSD to sections of rat and human brain was determined by liquid scintillation counting, indicated that the binding of [^{125}I]LSD reached equilibrium by 60 minutes at room tempera-

ture. Consequently, all tissue sections were incubated for 1 hour at 22°C, washed three times at 4°C for 20 minutes each, and dried under a stream of cool air.

To label 5-HT_{1A} receptors, the procedure of Pazos and associates (1987a) was followed with minor modifications (Hensler et al. 1991). The slide-mounted tissue sections were preincubated for 30 minutes in the incubation buffer. The sections were incubated with 2 nmol/L [^{3}H]8-OH-DPAT (158 Ci/mmol; DuPont New England Nuclear) in a buffer containing 4 mmol/L $CaCl_2$, 0.17 mol/L Tris-HCl buffer, 0.01% ascorbic acid, pH 7.6, and 10 μmol/L pargyline. Adjacent sections were incubated similarly but contained 5 μmol/L 5-HT for the definition of nonspecific binding. Incubations were carried out in a light-proof room for 1 hour at 22°C, washed twice for 5 minutes at 4°C in buffer, and washed for 10 seconds in H_2O at 4°C.

To visualize the 5-HT uptake sites located on 5-HT terminals, the radioligand [^{3}H]CN-IMI was used (Kovachich et al. 1988; Joyce et al. 1992). Slide-mounted tissue sections were preincubated for 10 minutes at 4°C in buffer. The sections were incubated with 0.5 nmol/L [^{3}H]CN-IMI (78.2 Ci/mmol, K_d = 0.14 nmol/L) in buffer containing 50 mmol/L Tris plus 150 mmol/L NaCl, pH 7.4. Adjacent sections were incubated similarly but contained 100 μmol/L desipramine for the definition of nonspecific binding. Incubations were carried

washed twice for 1 hour at 4°C in buffer, and 10 seconds in H_2O at 4°C.

In all cases, following drying under a stream of cool air, the sections were stored with desiccant at 4°C overnight to remove any remaining moisture. The slides were placed in x-ray cassettes and tightly apposed to Ultrofilm (Leica) for varying times at room temperature. Low or high activity ^{3}H-containing plastic standards (American Radiolabeled Chemicals, St. Louis, MO) were included with the tissue-mounted slides and apposed to film. Exposure times for each radioligand were as follows: [^{3}H]ketanserin-incubated sections for 1 to 2 months; [^{125}I]LSD-incubated sections for 72 hours; [^{3}H]8-OH-DPAT-incubated sections for 60 days; and [^{3}H]CN-IMI-incubated sections for 28 days. The film was then processed in Kodak GBX developer (3 minutes) and fixative (6 minutes).

Data Analysis

The illuminated image of each autoradiograph was collected by a video camera connected to an IBM AT-based image-analysis system (DUMAS, Drexel University, Philadelphia, PA). Because of nonlinearities in the film and image array processor, these original grey values were not a linear function of the concentration of radioligand. Tritium-embedded plastic standards containing high concentrations of tritium were calibrated against ^{125}I-containing tissue standards and used to transform the original grey value of each pixel to a linear function and expressed as the quantity of ^{125}I-radioligand bound (Artymyshyn et al. 1990). The digitized images of the autoradiographs of total and nonspecific binding were displayed, the region of interest outlined, and the density of bound radioligand displayed for the region. Nonspecific binding was subtracted from total binding to obtain specific binding. The tissue sections used for the autoradiographic image were stained for Nissl after the development of the autoradiographic images, making them available for the visualization of brain nuclei. In addition, every 20th section directly processed for Nissl staining was used to clarify anatomic boundaries. The autoradiographic image was viewed in one frame and the histologic material in the other to facilitate accurate analysis of brain regions. Regions of the cortex were identified using the atlas of Nieuwenhuis and associates (1978). The regions of the parahippocampus, including entorhinal cortex and subfields of the hippocampus were identified with the aid of the atlas of Amaral and Insausti (1990). For the detailed mapping of [^{3}H]CN-IMI binding in the striatum of control and schizophrenic cases additional information was obtained. Methods previously described for measuring the patch and matrix compartment-related binding of radioligands were used to delineate the pattern of [^{3}H]CN-IMI binding in striatum (Joyce et al. 1992). Briefly, microzones high in the density of binding sites and the region surrounding the microzones (low in density) were outlined in four regions of the striatum (dorsal caudate nucleus, dorsal putamen, nucleus accumbens, ventral putamen) for at least four serial sections. The average density of the binding in the microzones and "surround" was determined for each striatal region.

For mapping studies a minimum of four sections per level were analyzed by region of brain. Average values were pooled for all cases by disease (treatment condition). Both hemispheres were available for only a few cases. For this reason, each hemisphere was treated as an independent sample for analysis of differences. Differences in the binding of [^{3}H]ketanserin, [^{125}I]LSD, [^{3}H]8-OH-DPAT, and [^{3}H]CN-IMI between regions within disease groups and between disease groups were determined by two-factor analysis of variance with brain region as the repeated measure. Post-hoc paired comparisons were tested for significance of difference using the method of Duncan (Snedecor and Cochran, 1967). Because fewer regions of brain were available for the suicide group, post-hoc paired comparisons were limited to control versus schizophrenia and control versus suicide.

Materials

Drugs were obtained from the pharmaceutical company of origin or from commercial sources. All radioligands,

[^{3}H]ketanserin (61 Ci/mmol), [^{125}I]LSD (2200 Ci/mmol), [^{3}H]8-OH-DPAT (158 Ci/mmol), and [^{3}H]CN-IMI (78.2 Ci/mmol) were purchased from DuPont (New England Nuclear). The drugs mianserin (Organon, Oss, Netherlands), tripolidine (Sigma), prazosin (Sigma), ketanserin (Janssen, Beerse, Belgium), pargyline (Sigma), desipramine (Sigma), and 5-HT (Sigma) were obtained from their respective sources.

RESULTS

Preliminary experiments were performed to define optimal incubation procedures in which the binding of a range of concentrations of [^{3}H]ketanserin, [^{125}I]LSD, [^{3}H]8-OH-DPAT, and [^{3}H]CN-IMI to brain sections of rat ($n = 4$) and human frontal cortex ($n = 6$) was determined by liquid scintillation counting. The results indicated that the K_d values were similar in rat and human tissue, but the B_{max} values were lower in the human tissue sections. For binding of [^{3}H]ketanserin, [^{125}I]LSD, [^{3}H]8-OH-DPAT, and [^{3}H]CN-IMI to human tissue sections, the K_d values were, respectively, 0.81 nmol/L (range 0.41 to 1.1 nmol/L), 1.3 nmol/L (range 0.7 to 1.5 nmol/L), 0.6 nmol/L (range 0.4 to 1.5 nmol/L) and 0.14 nmol/L (range 0.08 to 0.15 nmol/L). Comparison of the distribution of the radioligands indicated a unique pattern for each site in control brains. In the following sections, results obtained for the control group will be compared to those obtained from the other experimental groups for the striatum, regions of cortex, and the parahippocampal region (including hippocampus).

Striatum

The number of [^{3}H]CN-IMI binding sites in the striatum of the control group was 5- to 10-fold higher than in any region of cortex ($p < .05$). The highest number of sites was found in the putamen, with values significantly higher than in the caudate or nucleus accumbens ($p < .05$; Fig. 2). The binding sites were particularly evident in the ventral putamen (Fig. 3A). As shown in Figure 3A, the topography of [^{3}H]CN-IMI binding sites in the putamen was patchy with regions of dense binding (microzones) surrounded by regions of less dense binding (Table 2). Microzones of dense binding were also visible in the caudate nucleus but less apparent. For the control group, the number of 5-HT$_{1A}$ receptors was considerably lower in the striatum than in the cortex (by 9- to 10-fold), and was homogeneously distributed (Figs. 2 and 3C). Serotonin$_2$ receptor sites labeled with [^{3}H]ketanserin (Figs. 2 and 3B) showed a relatively homogeneous distribution in the striatum. No significant difference in the amount of binding between the caudate, putamen, and nucleus accumbens was

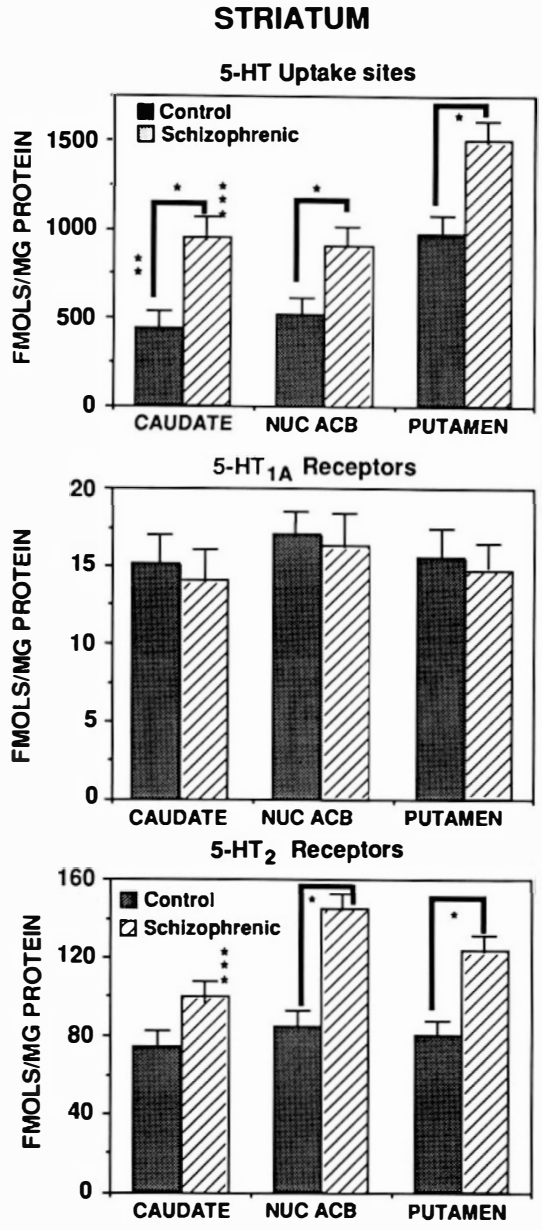

Figure 2. Bar graphs showing the mean number (± SD) o 5-HT uptakes sites labeled with [^{3}H]CN-IMI, 5-HT$_{1A}$ recep tors labeled with [^{3}H]8-OH-DPAT, and 5-HT$_2$ receptors la beled with [^{3}H]ketanserin for control and schizophreni groups for regions of the striatum. The schizophrenics showe significantly ($p < .01$ indicated by bar and asterisk) elevate numbers of 5-HT uptake sites (between group effects, $p < .01$ all regions) and 5-HT$_2$ receptors (between group effects, $p <$ .001; nucleus accumbens and putamen). For the schizophreni group 5-HT uptake sites were significantly higher in the puta men than the caudate or nucleus accumbens (between regions $p < .05$) and 5-HT$_2$ receptors were significantly higher in th nucleus accumbens and putamen than in the caudate (be tween regions, $p < .05$). Abbreviations: Nuc Acb, nucleus ac cumbens. Between group differences are indicated by a sin gle asterisk, significant differences between regions for contr group by double asterisk, and significant differences betwee regions for schizophrenic group by triple asterisk.

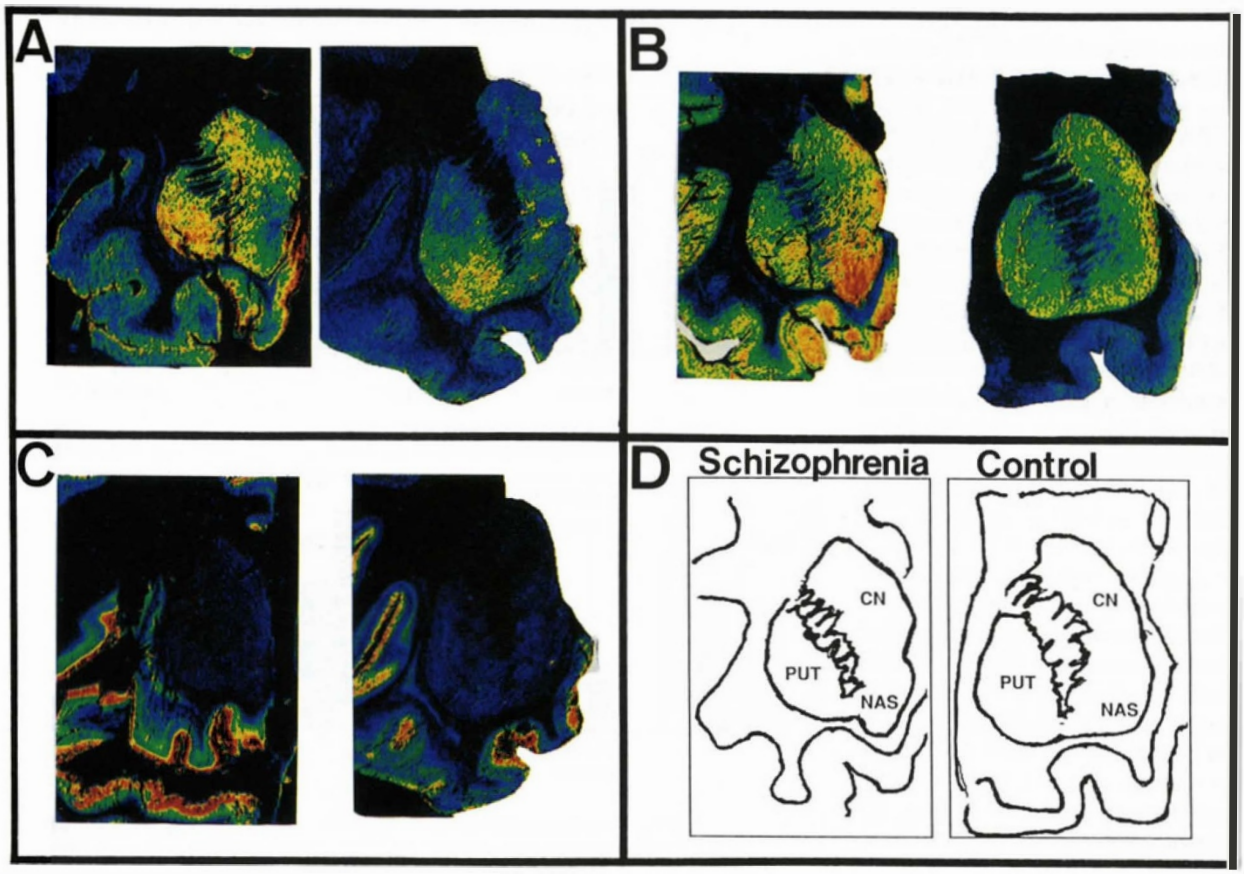

Figure 3. Pseudocolor images from autoradiographs representing the number of 5-HT uptake sites labeled with [^{3}H]CN-IMI (A), 5-HT_2 receptors labeled with [^{3}H]ketanserin (B), and 5-HT_{1A} receptors labeled with [^{3}H]8-OH-DPAT (C) for a control and a schizophrenic case for regions of the striatum. (D) The diagram of the striatum shows the location of the regions analyzed. Note larger zones of higher density of [^{3}H]CN-IMI sites in the schizophrenic case in the ventral striatum and the existence of "microzones" of dense binding in the dorsal striatum (caudate nucleus and putamen) of the schizophrenic but not the control case. In contrast, 5-HT_2 receptors are increased in the ventral striatum (nucleus accumbens and ventral putamen). The pseudocolor coding for the density of binding sites at a single concentration is represented by red as the highest. Abbreviations: Nuc Acb, nucleus accumbens.

found. Similar results were obtained with [^{125}I]LSD (data not shown). The number of sites labeled with a single concentration of [^{125}I]LSD was higher in the striatum than that found in the hippocampus and entorhinal cortex but lower than that observed in most regions of cortex ($p < .05$).

The striatum of the schizophrenic cases showed a different pattern of binding as compared to controls for [^{3}H]CN-IMI to 5-HT uptake sites and of [^{3}H]ketanserin binding to 5-HT_2 sites (Figs. 2 and 3). The number of 5-HT uptake sites was elevated in the striatum of the schizophrenic group by 60% to 100% as compared to the control group ($p < .01$). As depicted in Figure 3A, the typical pattern in the control cases of highest binding in the ventral putamen still existed in the schizophrenic cases. However, the microzones of binding were significantly denser and greater in size (Table 2). In addi-

Table 2. Binding of [^{3}H]CN-IMI to 5-HT Uptake Sites in Striatum[a]

Region	Entire Area	Surround	Microzone
Control			
Dorsal-Cd	476 ± 95	199 ± 59	637 ± 222[b]
Nuc Acb	529 ± 133	227 ± 91	736 ± 162[b]
Dorsal-PUT	424 ± 112	221 ± 92	633 ± 178[b]
Ventral-PUT	1035 ± 143	423 ± 232	1341 ± 193[b]
Schizophrenia			
Dorsal-Cd	988 ± 143[3]	221 ± 72	1037 ± 193[b,c]
Nuc Acb	839 ± 133[3]	318 ± 99	1056 ± 204[b,c]
Dorsal-PUT	1029 ± 222[3]	299 ± 102	1639 ± 203[b,c]
Ventral-PUT	1646 ± 143[3]	421 ± 273	1965 ± 213[b,c]

[a] Values are presented as means ± SD fmol/mg protein, $n = 8$ for control and $n = 10$ for schizophrenics.
[b] $p < .05$ versus surround and entire area.
[c] $p < .05$ versus control.

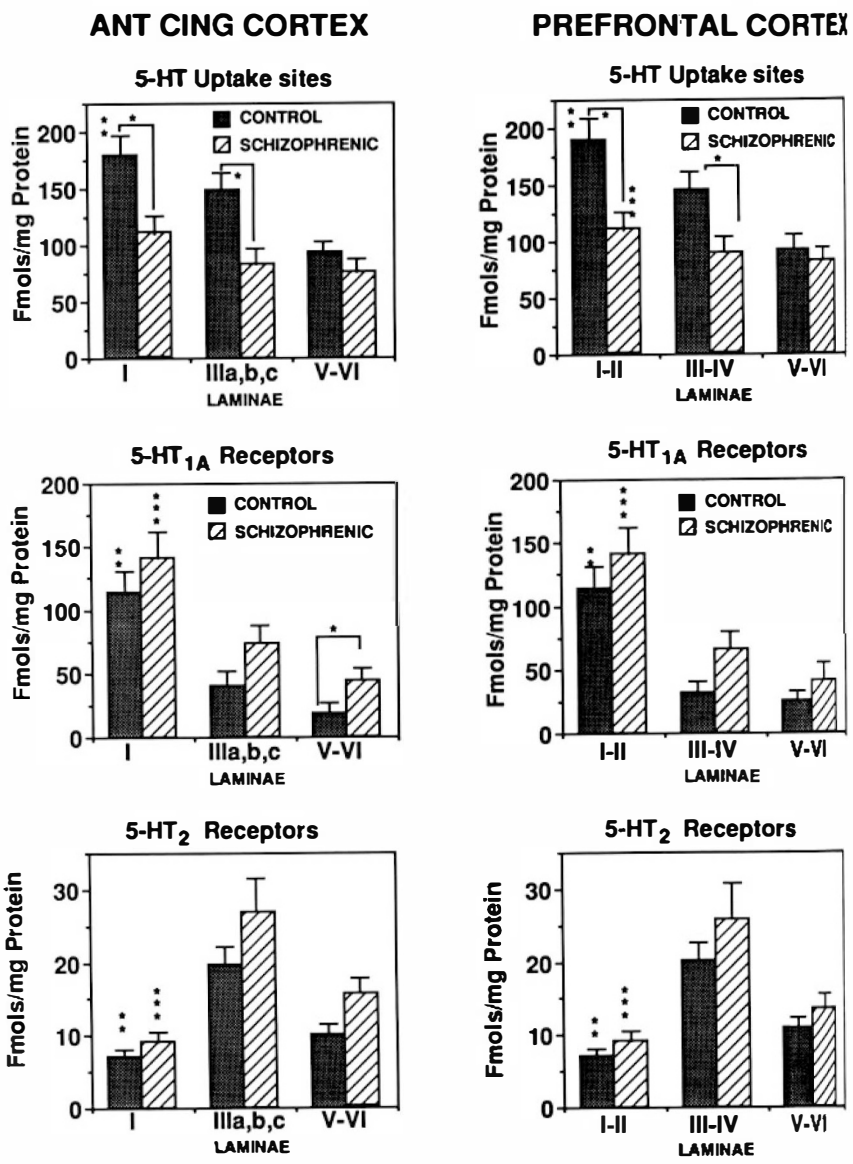

Figure 4. Bar graphs showing the mean number (± SD) number of 5-HT uptake sites labeled with [^{3}H]CN-IMI (top), 5-HT$_{1A}$ receptors labeled with [^{3}H]8-OH-DPAT (middle), and 5-HT$_2$ receptors labeled with [^{125}I]LSD (bottom) for control and schizophrenic groups for regions of the anterior cingulate cortex (ANT CING CORTEX) and prefrontal cortex. The locations of the regions analyzed are shown in Figure 1A. The schizophrenics showed reduced numbers of 5-HT uptake sites in laminae I–III of the anterior cingulate cortex (between groups, $p < .01$) and of laminae I–IV of prefrontal cortex (between groups, $p < .01$) as compared to the control group. The number of 5-HT$_{1A}$ receptors was elevated in the laminae V–VI of the anterior cingulate cortex as compared to the control group (between groups, $p < .01$). For the control group, 5-HT uptake sites were significantly higher in laminae I–III than laminae V–VI (between regions, $p < .01$), 5-HT$_{1A}$ receptors were higher in laminae I–II than III–VI (between regions, $p < .01$), and 5-HT$_2$ receptors higher in laminae III than all other laminae ($p < .001$). For the schizophrenic group, 5-HT$_{1A}$ receptors were higher in laminae I–II than III–VI (between regions, $p < .01$), and 5-HT$_2$ receptors higher in the intermediate laminae (IIIa,b,c, or III–IV) than all other laminae ($p < .001$). Between group differences are indicated by single asterisk, significant differences between regions for control group by double asterisk, and significant differences between regions or schizophrenic group by triple asterisk.

tion, microzones of dense binding were frequently observed in the dorsal putamen and in the caudate nucleus in the schizophrenics but not in the controls. The binding in the microzones, and not in the surrounding matrix, was significantly higher in the schizophrenics as compared to the controls in all regions of the striatum ($p < .01$, Table 2). Binding of [^{3}H]ketanserin (Figs. 2B and 3) and [^{125}I]LSD (not shown) for 5-HT$_2$ sites was also elevated and the pattern of expression altered. Thus, the number of sites was significantly higher in the schizophrenic cases than the control cases in the nucleus accumbens ($p < .001$) and putamen ($p < .001$), but not for the caudate nucleus (Fig. 2B). The results of the saturation experiments indicated that the K_d values for [^{125}I]LSD binding to 5-HT$_2$ sites in the striatum of control and schizophrenic groups was similar and the values for the B_{max} altered ($p < .01$). The control group had a K_d value of 1 nmol/L (range 0.7 to 1.5 nmol/L) with a mean B_{max} of 62 ± 13 (SD) fmols/mg protein. The schizophrenic group had a K_d of 1.4 nmol/L (0.8 to 1.5 nmol/L) and a B_{max} of 117 ± 12 fmols/mg protein. No difference was observed for [^{3}H]8-OH-DPAT binding to 5-HT$_{1A}$ receptors in schizophrenic cases as compared to controls (Figs. 2C and 3).

Frontal, Premotor, and Motor Cortex

For regions of cortex in control cases, [^{3}H]CN-IMI labeling of 5-HT uptake sites was highest in the external laminae (laminae I and II) and lowest in laminae V and VI (Figs. 4 and 5). This pattern was most con-

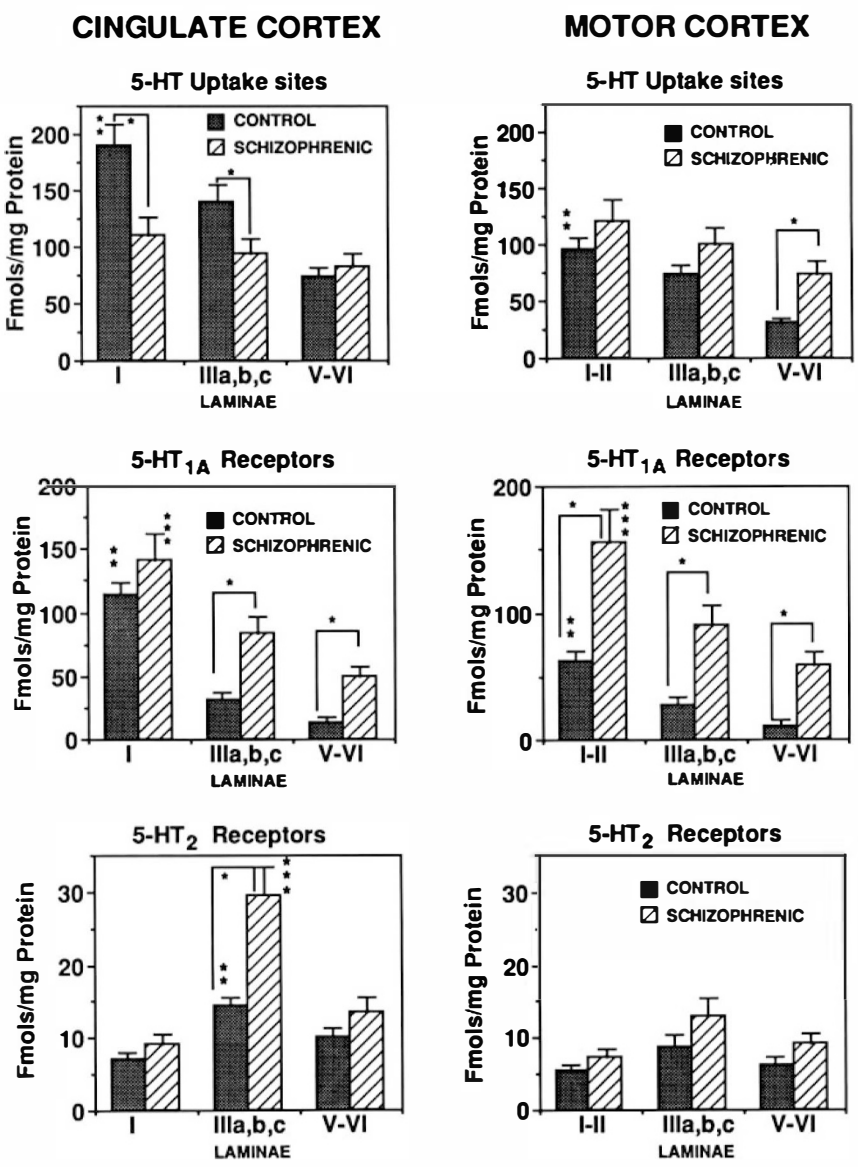

Figure 5. Bar graphs showing the mean number (± SD) of 5-HT uptake sites labeled with [^{3}H]CN-IMI, 5-HT$_{1A}$ receptors labeled with [^{3}H]8-OH-DPAT, and 5-HT$_2$ receptors labeled with [^{125}I]LSD for control and schizophrenic groups for regions of the cingulate cortex and motor cortex. The locations of the regions analyzed are shown in Figure 1C. The schizophrenic group showed reduced numbers of 5-HT uptake sites in the laminae I–III of posterior cingulate cortex ($p < .001$) and an elevation in the deep laminae of the motor cortex ($p < .01$) as compared to the control group. The schizophrenic group showed elevated numbers of 5-HT$_{1A}$ receptors in the laminae III and V–VI of posterior cingulate cortex ($p < .01$) and all laminae of motor cortex ($p < .001$) as compared to the control group. The number of 5-HT$_2$ receptors was elevated in the schizophrenic group in laminae III of posterior cingulate cortex ($p < .001$) as compared to the control group. Within the cingulate cortex, the control group showed higher numbers of 5-HT uptake sites for laminae I–II than IIIa,b,c, which is greater than laminae V-VI (between regions, $p < .01$). Serotonin$_{1A}$ receptors were higher in laminae I–II than IIIa,b,c, which is greater than laminae V-VI (between regions, $p < .01$), and 5-HT$_2$ receptors higher in laminae III than all other laminae ($p < .001$). For the schizophrenic group, 5-HT$_{1A}$ receptors were higher in laminae I–II than III–VI (between regions, $p < .01$), and 5-HT$_2$ receptors higher in laminae IIIa,b,c than all other laminae ($p < .001$). Within the motor cortex, the control group showed lower numbers of 5-HT uptake sites for laminae V–VI than all other laminae (between regions, $p < .01$). Serotonin$_{1A}$ receptors were higher in laminae I–II than IIIa,b,c, which is greater than laminae V–VI (between regions, $p < .01$). For the schizophrenic group, 5-HT$_{1A}$ receptors were higher in laminae I–II than IIIa,b,c, which is greater than laminae V-VI (between regions, $p < .01$). Abbreviations: CINGULATE CORTEX, posterior cingulate cortex. Between group differences are indicated by single asterisk, significant differences between regions for control group by double asterisk, and significant differences between regions for schizophrenic group by triple asterisk.

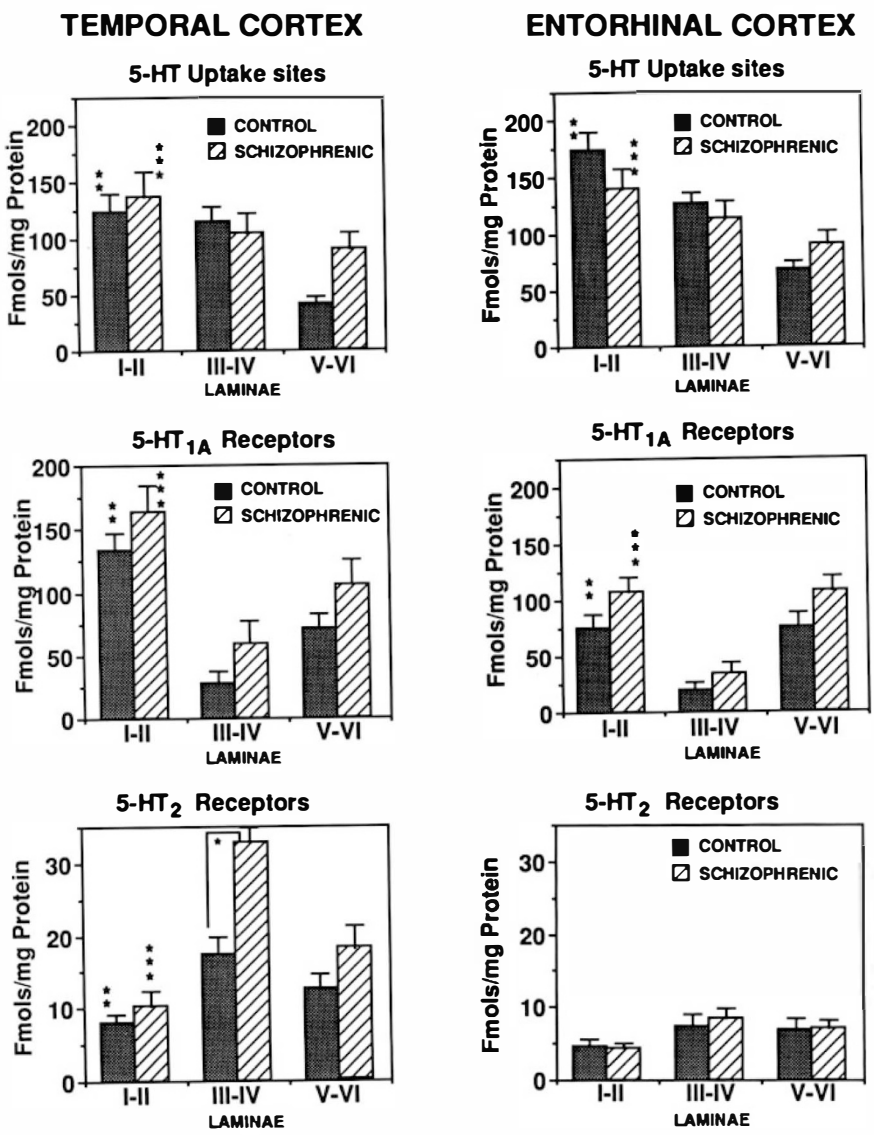

Figure 6. Bar graphs showing the mean number (± SD) of 5-HT uptake sites labeled with [^{3}H]CN-IMI, 5-HT$_{1A}$ receptors labeled with [^{3}H]8-OH-DPAT, and 5-HT$_2$ receptors labeled with [^{125}I]LSD for control and schizophrenic groups for regions of the temporal cortex and entorhinal cortex. The locations of the regions analyzed are shown in Figure 1C. The schizophrenic group showed elevated numbers of 5-HT$_2$ receptors in laminae III–IV of the temporal cortex (between group, $p < .001$). Within the temporal cortex, the control group exhibited higher numbers of 5-HT uptake sites for laminae I–II than III–IV, which was greater than laminae V–VI (between regions, $p < .01$). Serotonin$_{1A}$ receptors were higher in laminae I–II than V–VI, which is greater than laminae III–IV (between regions, $p < .01$), and 5-HT$_2$ receptors were higher in laminae III–IV than all other laminae ($p < .001$). For the schizophrenic group, 5-HT$_{1A}$ receptors were higher in laminae I–II than V–VI, which is greater than laminae III–IV (between regions, $p < .01$), and 5-HT$_2$ receptors were higher in laminae III–IV than V–VI, which is higher than laminae I–II ($p < .01$). Within the entorhinal cortex, the control group showed higher numbers of 5-HT uptake sites in laminae I–II than III–IV, which is greater than laminae V–VI (between regions, $p < .01$). Serotonin$_{1A}$ receptors were lower in laminae III–IV than I–II or V–VI (between regions, $p < .01$). For the schizophrenic group, 5-HT uptake sites were higher in laminae I–IV than V–VI (between regions, $p < .01$), 5-HT$_{1A}$ receptors were lower in laminae III–IV than I–II or V–VI (between regions, $p < .01$). Between group differences are indicated by single asterisk, significant differences between regions for control group by double asterisk, and significant differences between regions for schizophrenic group by triple asterisk.

spicuous in the anterior cingulate (laminae I > laminae V–VI; $p < .01$), frontal (laminae I–II > III–IV > V–VI; $p < .01$), posterior cingulate (laminae I > III–IV > V–VI; $p < .01$), and parietal cortices (data not shown) and least distinct in motor cortex (laminae I–II > V–VI; $p < .01$). In most of the cortices the pattern of [^{3}H]8-OH-DPAT binding of 5-HT$_{1A}$ receptors closely followed that of the 5-HT uptakes sites with [^{3}H]8-OH-DPAT binding

to 5-HT_{1A} receptors highest in the upper laminae, being more than twofold greater in number than the middle and inner laminae (Figs. 4 and 5). This was evident in the anterior cingulate (laminae I > laminae V–VI; $p < .01$), frontal (laminae I–II > III–IV = V–VI; $p < .01$), posterior cingulate (laminae I > III–IV > V–VI; $p < .01$), and parietal (laminae I > III–IV > V–VI; $p < .01$, data not shown) cortices, but less so for the motor cortex (laminae I–II > III > V–VI; $p < .05$). The labeling of 5-HT_2 receptors with [^{125}I]LSD was more than twofold higher in the middle laminae (layers III and IV) than the deep laminae and slightly higher in the deep than the superficial laminae of anterior cingulate ($p < .001$), frontal ($p < .001$), posterior cingulate ($p < .05$), and parietal ($p < .05$) cortices. In motor cortex the pattern of 5-HT_2 receptors did not differ by laminae (Fig. 5).

For the schizophrenic cases, binding of [^{3}H]CN-IMI to 5-HT uptake sites was reduced by 51% to 76% as compared to control cases in the external and middle laminae of some cortical regions, including the anterior cingulate (schizophrenic < control; $p < .01$; Fig. 4), frontal cortex (schizophrenic < control; $p < .01$; Fig. 4), and posterior cingulate (schizophrenic < control; $p < .01$; Fig. 5), but not in the motor cortex or parietal cortex (or temporal cortex, see below). Consequently, there was no significant difference among laminae of the anterior cingulate, frontal cortex, and posterior cingulate cortices of the schizophrenic group. Comparison of the schizophrenic to the control group demonstrated better than a threefold elevation in the binding of [^{3}H]8-OH-DPAT binding to 5-HT_{1A} receptors in the cingulate (schizophrenic > control; $p < .01$; Figs. 4 and 5) and motor cortex (schizophrenic > control; $p < .001$; Fig. 5) but not in the frontal (Fig. 4), or parietal cortices (or temporal cortex, see below). In the anterior cingulate, the increase was significant only for the deep laminae ($p < .01$), whereas both middle and deep laminae of the posterior cingulate showed better than twofold higher numbers of 5-HT_{1A} receptors ($p < .01$) in the schizophrenic group as compared to the control group. All laminae of the motor cortex show two- to threefold increases in binding of [^{3}H]8-OH-DPAT ($p < .01$) in the schizophrenic group as compared to the control group. However, the laminar arrangement of 5-HT_{1A} receptors was not altered in any cortical region of the schizophrenic cases. [^{125}I]LSD binding to 5-HT_2 sites was also elevated in the middle laminae of the posterior cingulate (schizophrenic > control; $p < .001$; Fig. 5) but not in the frontal, anterior cingulate, or motor cortices.

Temporal Cortex and Hippocampus

In most regions of the temporal lobe of the control cases, the pattern of 5-HT uptake sites was similar to that in frontal cortex with the external laminae exhibiting the highest binding of [^{3}H]CN-IMI (laminae I–II > V–VI; $p < .01$). In the superior, middle, and inferior lobes of the temporal cortex, the binding of [^{3}H]8-OH-DPAT was trilaminar with the binding highest in the external laminae and lowest in the middle laminae (laminae I–II > V–VI > III; $p < .01$; Fig. 6). As in the frontal cortex, [^{125}I]LSD-labeled 5-HT_2 receptors were highest in number in the middle laminae (laminae III–IV > I–II = V–VI; $p < .01$; Fig. 6). In the medial temporal lobe of the control cases (entorhinal cortex) [^{3}H]CN-IMI binding to 5-HT uptake sites was most abundant in number in the external laminae and the relative numbers similar to other regions of temporal cortex (laminae I–II > V–VI; $p < .01$; Fig. 6). In contrast, the laminar distribution of 5-HT_2 receptors in this same region was indistinct with relatively low numbers of sites when compared to other regions of temporal cortex (Fig. 6). The binding of [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors was nearly equivalent in the upper and deep laminae and quite low in the middle laminae of the entorhinal cortex (laminae III, IV > I, II and V–VI; $p < .01$; Fig. 6). The binding in the region immediately adjacent to the entorhinal cortex, the perirhinal or lateral occipitotemporal cortex, showed significantly higher binding of both [^{3}H]8-OH-DPAT (laminae I–II > V–VI > III; $p < .01$) and [^{125}I]LSD (laminae III–IV > I–II = V–VI; $p < .001$) with patterns similar to the remainder of the temporal cortex.

The pattern of an overlapping organization of 5-HT_{1A} receptors and 5-HT uptake sites as well as a complementary organization of 5-HT_{1A} receptors and 5-HT_2 receptors, observable in most cortical regions of control cases, was not observed in the hippocampus. There appeared to be a reverse pattern of 5-HT uptake sites and 5-HT receptors, which was particularly evident for the distribution of 5-HT_{1A} receptors as compared to 5-HT uptake sites (Fig. 7). Regions of the parahippocampus and hippocampus that were low in the number of [^{3}H]CN-IMI-labeled sites (Figs. 7A and 9), such as the subiculum and CA_1 subfield, were highest in the number of 5-HT_{1A} receptors labeled with [^{3}H]8-OH-DPAT (Figs. 7C, 8B, and 9). Conversely, in the dentate gyrus (DG), relatively high numbers of 5-HT uptake sites and low numbers of 5-HT_{1A} receptors were apparent. Thus, [^{3}H]CN-IMI-labeled sites were significantly higher in the DG than the CA_3 or CA_1 subfields ($p < .01$), and [^{3}H]8-OH-DPAT binding was higher in the CA_1 than DG ($p < .01$). The distribution of 5-HT_2 receptors largely paralleled that of 5-HT_{1A} receptors in the main body of the hippocampus (Figs. 8A and 9), but not in the rostral hippocampus (Fig. 7B). In the rostral hippocampus, low levels of [^{125}I]LSD binding were present and inverse patterns to that of [^{3}H]8-OH-DPAT binding. In contrast, in the main body of the hippocampus relatively high numbers of 5-HT_{1A} receptors and 5-HT_2 receptors were found in the pyramidal layer of the CA_1 subfield, lower in stri-

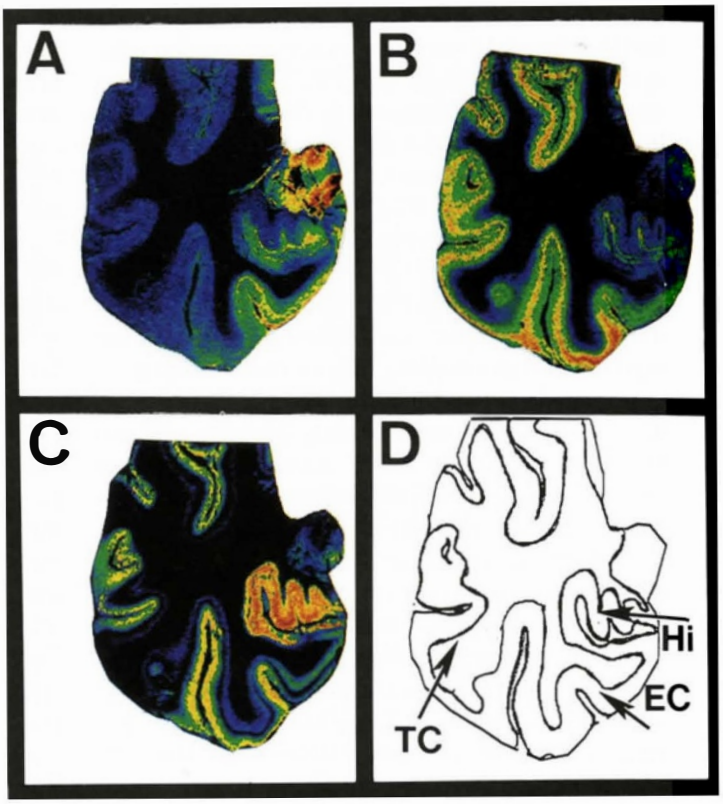

Figure 7. Pseudocolor images from autoradiographs representing the number of 5-HT uptake sites labeled with [^{3}H]CN-IMI (A), 5-HT$_2$ receptors labeled with [^{125}I]LSD (B), and 5-HT$_{1A}$ receptors labeled with [^{3}H]8-OH-DPAT (C) for a control case for regions of the rostral hippocampus. (D) The diagram of the hippocampus shows the locations of the regions analyzed. The pseudocolor coding for the number of binding sites at a single concentration is represented by red as the highest. Note that in the entorhinal cortex, the density of receptors is low and the number of uptake sites relatively high, but in the CA1 subfield of the hippocampus, the opposite pattern exists with [^{3}H]8-OH-DPAT-labeled 5-HT$_{1A}$ receptors high in number and 5-HT uptake sites low. However, 5-HT$_2$ receptors in the rostral hippocampus were low in number and the pattern inverse to that of [^{3}H]8-OH-DPAT binding (this figure) but overlap with 5-HT$_{1A}$ receptors in more caudal regions of the hippocampus (see Fig. 8). Abbreviations: EC, entorhinal cortex; Hi, hippocampus; TC, temporal cortex.

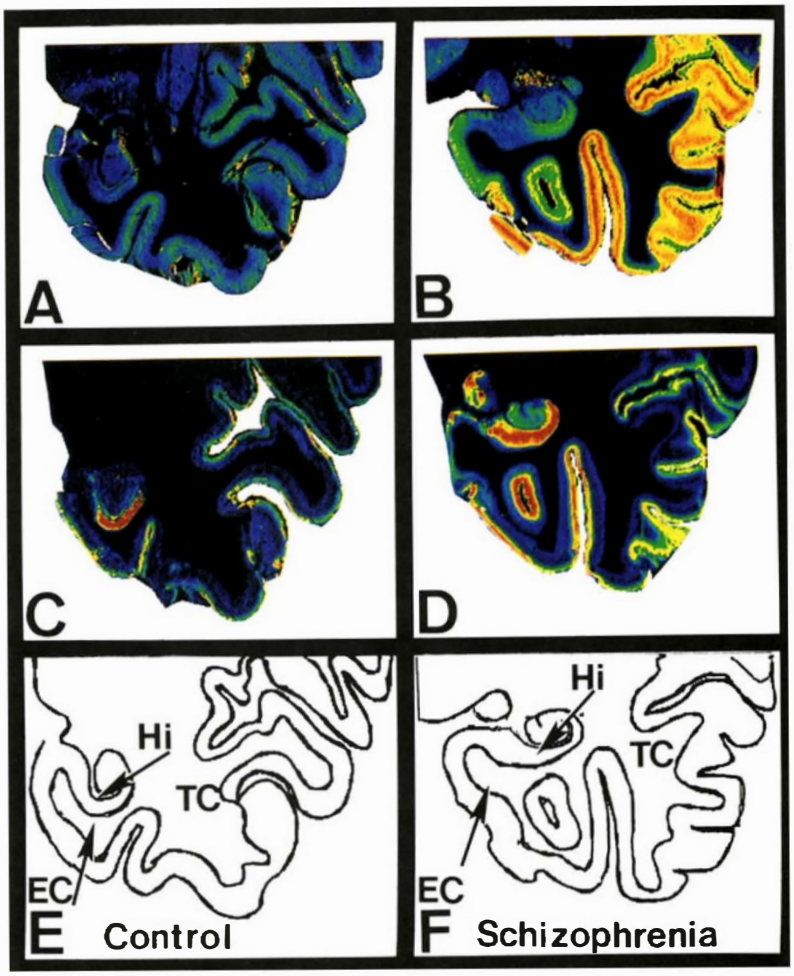

Figure 8. Pseudocolor images from autoradiographs representing the relative number of 5-HT$_{1A}$ receptors labeled with [^{3}H]8-OH-DPAT (A, B) and 5-HT$_2$ receptors labeled with [^{125}I]LSD (C, D), for a control case (A, C) and for a schizophrenic case (B, D) for hippocampus and temporal cortex. The diagrams (E, F) of the temporal cortex, parahippocampus, and hippocampus show the locations of the regions analyzed. Note the marked elevation of 5-HT$_2$ receptors in the temporal cortex, the smaller elevation in the hippocampus, and no change in the entorhinal cortex of the schizophrenic group. The number of 5-HT$_{1A}$ receptors was elevated in the hippocampus, particularly the DG, but not in the entorhinal cortex or temporal cortex. The pseudocolor coding for the number of binding sites at a single concentration is represented by red as the highest. Abbreviations: EC, entorhinal cortex, Hi, hippocampus; TC, temporal cortex.

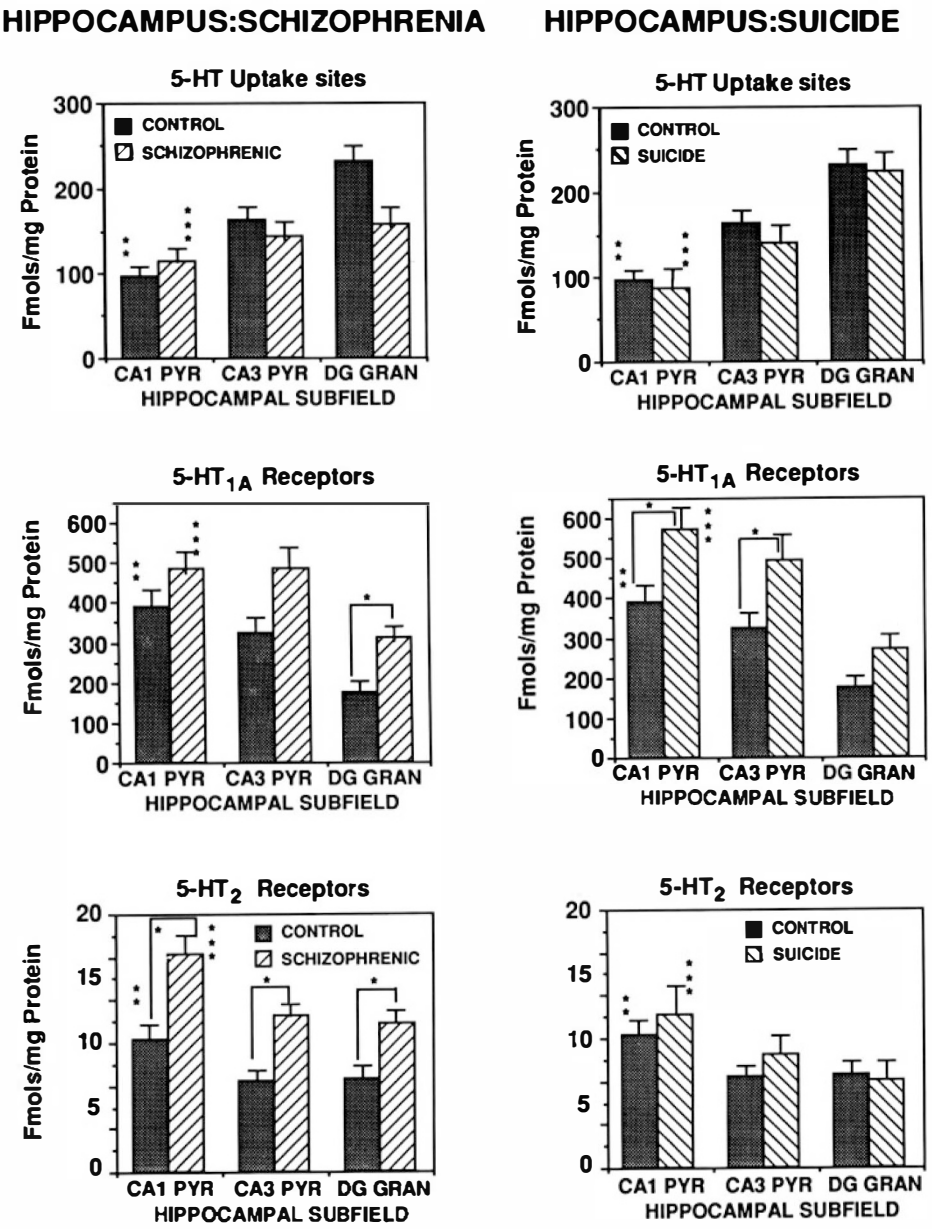

Figure 9. Bar graphs showing the mean number (± SD) of 5-HT uptake sites labeled with [^{3}H]CN-IMI, 5-HT$_{1A}$ receptors labeled with [^{3}H]8-OH-DPAT, and 5-HT$_2$ receptors labeled with [^{125}I]LSD for control and schizophrenic (left panel), and for control and suicide groups (right panel) for regions of the hippocampus. The locations of the regions analyzed are shown in Figure 1D. The schizophrenic group exhibited elevated numbers of 5-HT$_2$ receptors in all hippocampal subfields (between groups, $p < .01$) and 5-HT$_{1A}$ receptors in the DG (between groups, $p < .01$) of the hippocampus as compared to the control group. The suicide group showed increases in 5-HT$_{1A}$ receptors in subfields CA$_1$–CA$_3$ as compared to the control group (between groups, $p < .01$). The control group had higher numbers of 5-HT uptake sites in DG than CA$_3$, which is higher than CA$_1$, higher numbers of 5-HT$_{1A}$ receptors in CA$_1$ than CA$_3$, which is higher than DG, and higher numbers of 5-HT$_2$ receptors in CA$_1$ than all hippocampal subfields (between regions, $p < .01$). The schizophrenic group showed fewer 5-HT uptake sites in the CA$_1$ than all other hippocampal subfields, fewer 5-HT$_{1A}$ receptors in DG than all other hippocampal subfields, and higher numbers of 5-HT$_2$ receptors in CA$_1$ than all hippocampal subfields (between regions, $p < .01$). The suicide group demonstrated higher numbers of 5-HT uptake sites in DG than CA$_3$, which is higher than CA$_1$, fewer numbers of 5-HT$_{1A}$ receptors in DG than all hippocampal subfields, and higher numbers of 5-HT$_2$ receptors in CA$_1$ than all hippocampal subfields (between regions, $p < .01$). The number of sites for the pyramidal cell layer of CA$_1$ (CA$_1$ PYR) and CA$_3$ (CA$_3$ PYR) is shown, and the granule cell layer of the dentate gyrus (DG GRAN). Between group differences are indicated by single asterisk, significant differences between regions for control group by double asterisk, and significant differences between regions for the schizophrenic (left panel) or suicide (right panel) groups by triple asterisk.

atum oriens, and lowest in the CA_3 subfield and DG (compare Figs. 7 and 8). To determine if this inconsistency between the rostral and main body of the hippocampus reflected labeling of sites other than 5-HT_2 receptors by [^{125}I]LSD, the binding of [^{3}H]ketanserin and [^{125}I]LSD for 5-HT_2 sites was compared. Only in the molecular layer of the DG and moleculare radiatum of the CA_1 of the hippocampus was the binding of [^{125}I]LSD not displaced by ketanserin, nor was there significant [^{3}H]ketanserin binding. Thus, if anything, the amount of 5-HT_2 receptors was overestimated in the DG with [^{125}I]LSD. Therefore, the observed differences in the degree of overlap for 5-HT_{1A} receptors and 5-HT_2 receptors in the rostral and midbody of the hippocampus must be accounted for by other factors.

The schizophrenic and suicide cases were compared with the controls for the number of sites labeled with [^{125}I]LSD, [^{3}H]8-OH-DPAT, and [^{3}H]CN-IMI in the temporal cortex and hippocampus. Labeling of 5-HT uptake sites with [^{3}H]CN-IMI was not reduced in the temporal cortex (Fig. 6), entorhinal cortex (Fig. 6), or hippocampus (Fig. 9) of the schizophrenic cases as compared to control cases. In contrast, 5-HT uptake sites were significantly reduced in number for the suicide group as compared to the control group within the temporal cortex (suicide < control; $p < .01$; Fig. 10) and entorhinal cortex (suicide < control; $p < .01$; Fig. 10). The reduction in the suicide cases was significant only for the upper and middle laminae of the temporal cortex ($p < .01$). Although [^{3}H]8-OH-DPAT binding to 5-HT_{1A} receptors was unchanged in the temporal cortex of schizophrenics (Fig. 6) and suicide cases (Fig. 10) as compared to the controls, there was an elevation in the entorhinal cortex of the suicide cases as compared to controls (suicide > control; $p < .001$; Fig. 10). The increase in [^{3}H]8-OH-DPAT binding was significant for all laminae of the temporal cortex ($p < .001$). The number of 5-HT_{1A} receptors was increased in the hippocampus of schizophrenic and suicide cases as compared to controls (Fig. 9), but the patterns of increased binding were not similar in the schizophrenic and suicide cases. The increase in 5-HT_{1A} receptors was significant for the DG of the schizophrenic group as compared to the control group ($p < .01$) and for the CA_1–CA_3 subfields of the suicide group as compared to the control group ($p < .01$). The schizophrenic cases showed an elevation in 5-HT_2 receptors (Fig. 8) in the middle laminae of the temporal cortex (schizophrenia > control; $p < .05$; Fig. 6) and hippocampus as compared to controls (schizophrenia > control; $p < .01$; Fig. 9) but not in the entorhinal cortex (Figs. 6 and 8). Saturation assays of the binding of [^{125}I]LSD to 5-HT_2 receptors in the temporal cortex of the schizophrenic cases and controls indicated that the differences were due to a change in the number of sites (B_{max} 187 ± 31 fmols/mg protein for control; B_{max} 252 ± 37 fmols/mg protein for schizophrenia; $p < .01$) and not in the affinity of the 5-HT_2 receptors for [^{125}I]LSD binding (1.3 ± 0.4 nmol/mg for control, 1.9 ± 0.6 nmol/mg for schizophrenia). The suicide cases did not show alterations in the binding of [^{125}I]LSD to 5-HT_2 receptors as compared to controls (Figs. 9 and 10).

DISCUSSION

Striatum

The distribution of 5-HT_{1A} and 5-HT_2 receptors has been well characterized in human brain (Dillon et al. 1991; Hoyer et al. 1986; Pazos et al. 1987a, 1987b; Schotte et al. 1983) and nonhuman primate brain (Lidow et al. 1989). We obtained a K_d value for [^{3}H]8-OH-DPAT labeling of 5-HT_{1A} receptors that was only slightly lower than values obtained using sections of rat brain (Vergé et al. 1986). Other investigators have also found a lower K_d for the binding of [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors in sections of rat or human brain than that obtained with membrane preparations (Dillon et al. 1991; Hashimoto et al. 1991). We have also found that the binding of [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors in sections of human brain was completely inhibited by guanosine triphosphate (JN Joyce, A Shane and SJ Kim, unpublished findings), in contrast to what was observed in membranes derived from human brain (Hashimoto et al. 1991). This suggests that the linkage to G proteins is functionally intact in tissue sections (De Vivo and Maayani 1990). As expected, we obtained very low binding of [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors in the striatal complex (Pazos et al. 1987a). We examined the distribution of the 5-HT_2 receptor in tissue sections with [^{3}H]ketanserin and [^{125}I]LSD. We obtained K_d values for [^{3}H]ketanserin binding similar to those reported by Biegon and associates (1986) and Lidow and associates (1989), but lower than that reported by Hoyer and associates (1986). The K_d value we determined for [^{125}I]LSD binding to tissue sections is also similar to that reported by Arango and associates (1990) for human cortical membranes and Engel and associates (1984) for rat cortical membranes. The number of sites labeled with [^{125}I]LSD or [^{3}H]ketanserin in the striatum was significantly less than that labeled in the frontal cortex. This is consistent with previous studies that show two- to threefold higher densities in the isocortex than in the basal ganglia and hippocampus (Pazos et al. 1987b; Schotte et al. 1983). We did not find a heterogeneous pattern of 5-HT_{1A} or 5-HT_2 receptors in the striatum, unlike that for DA receptors (Joyce et al. 1986, 1988, 1991), muscarinic receptors (Lowenstein et al. 1990), and β-adrenergic receptors (Joyce et al. 1992).

Autoradiographic studies of the distribution of 5-HT uptake studies in human brain have been published using [^{3}H]imipramine (Cortés et al. 1988; Gross-

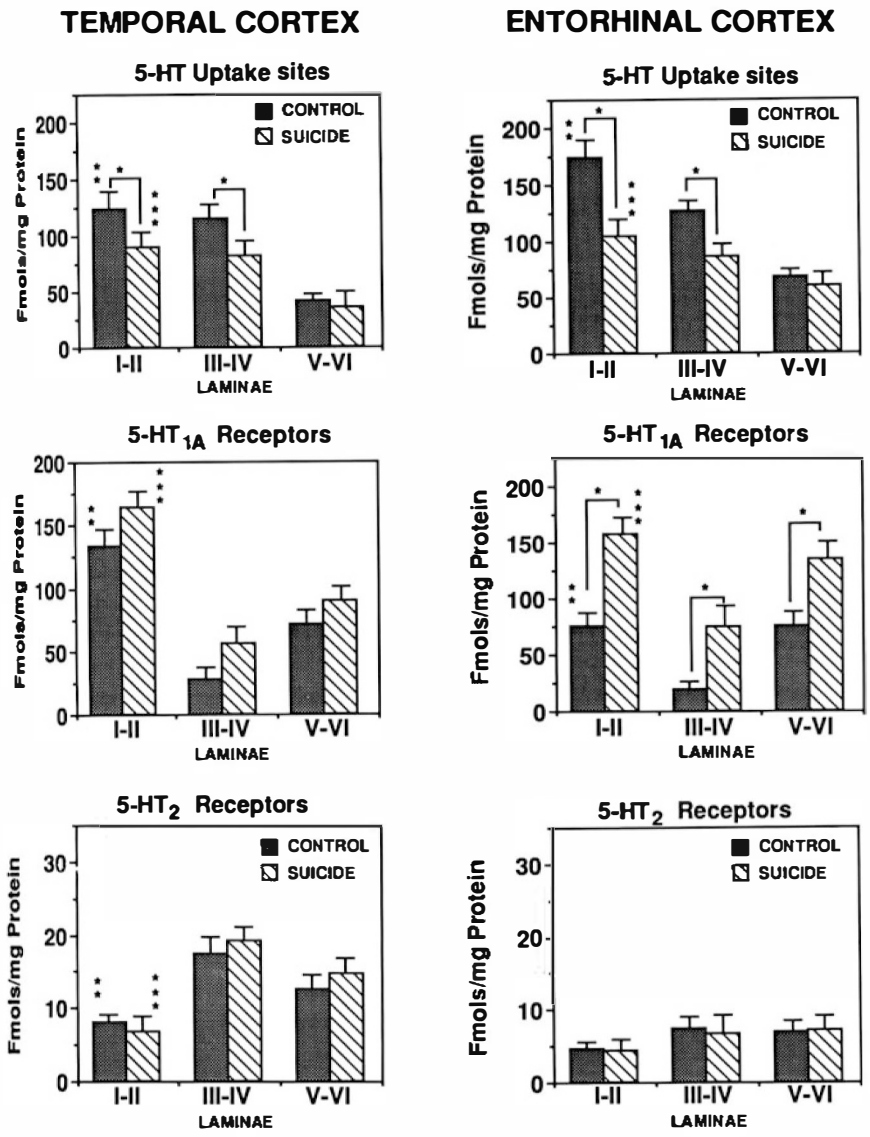

Figure 10. Bar graphs showing the mean number (± SD) of 5-HT uptake sites labeled with [^{3}H]CN-IMI (A), 5-HT$_{1A}$ receptors labeled with [^{3}H]8-OH-DPAT (B), and 5-HT$_2$ receptors labeled with [^{125}I]LSD (C) for control and suicide groups for regions of the temporal cortex and entorhinal cortex. The locations of the regions analyzed are shown in Figure 1C. The suicide group showed reduced numbers of 5-HT uptake sites in laminae I–IV of the temporal cortex and entorhinal cortex (between group, $p < .01$). The suicide group demonstrated elevated numbers of 5-HT$_{1A}$ receptors in all laminae and entorhinal cortex (between group, $p < .001$). Within the temporal cortex, the suicide group showed higher numbers of 5-HT uptake sites for laminae I–IV than V–VI (between regions, $p < .01$). Serotonin$_{1A}$ receptors were higher in laminae I–II than V–VI, which is greater than laminae III–IV (between regions, $p < .01$), and 5-HT$_2$ receptors were higher in laminae III–IV than all other laminae ($p < .01$). Within the entorhinal cortex, the suicide group showed higher numbers of 5-HT uptake sites in laminae I–IV than laminae V–VI (between regions, $p < .01$). Serotonin$_{1A}$ receptors were lower in laminae III–IV than I–II or V–VI (between regions, $p < .01$). Between group differences are indicated by single asterisk, significant differences between regions for control group by double asterisk, and significant differences between regions for suicide group by triple asterisk.

Isseroff and Biegon 1988) and [^{3}H]desmethylimipramine (Gross-Isseroff et al. 1988), but the information provided is limited as the radioligands do not selectively label 5-HT uptake sites (D'Amato et al. 1987). Only one study has described the autoradiographic distribution of the selective radioligand [^{3}H]paroxetine in human brain and the regions utilized were quite limited in scope (Cortés et al. 1988). The radioligand [^{3}H]CN-IMI does selectively label 5-HT uptake sites located on nerve terminals and the cell body (Kovachich et al. 1988) as exemplified by the loss of sites with selective lesions of 5-HT cell bodies (Hensler et al. 1991), and correlation with 5-HT levels and other radioligands that label the 5-HT transporter (Kovachich et al. 1988). Our results show that the distribution of [^{3}H]CN-IMI binding in human brain was highest in the striatal complex, consistent with previous reports of [^{3}H]paroxetine binding (Laruelle and Maloteaux 1989; Lawrence et al. 1990). The autoradiographs showed a heterogeneous pattern in the striatum, with microzones of dense [^{3}H]CN-IMI binding evident in the ventral striatum, where the dense microzones were 1.5 to 2 times denser than in the areas surrounding the microzones. These microzones were infrequently observed in the dorsal caudate nucleus and dorsal putamen. This corresponds to what has been observed by 5-HT immunocytochemical demonstration of the serotoninergic innervation of the monkey striatum (Lavoie and Parent 1990). The patchy organization of the serotonin uptake sites is related to an intrinsic neurochemical organization of the striatum, termed the striosomal and matrix compartments, which can be related to heterogeneities in the binding of a number of markers for transmitter systems (Joyce et al. 1988, 1992).

We observed significant changes in the pre- and postsynaptic components of the 5-HT system in the

schizophrenic striatum. A large increase in the number of 5-HT uptake sites was observed in all regions of the striatum and two striking changes were observed: (1) an increase in the number and density of patches in the ventral striatum, and (2) the appearance of patches of dense binding in the dorsal putamen and caudate nucleus. Since we used a concentration of [^{3}H]CN-IMI approximately three times the K_d (as determined in control tissue), it was unlikely that the changes observed in the schizophrenic cases were due to changes in the affinity of the radioligand for the uptake sites. The change in the number of uptake sites is consistent with previous evidence that there was an increase in the concentrations of 5-HT and/or 5-HIAA in the putamen of schizophrenic cases (Crow et al. 1979; Farley et al. 1980; Korpi et al. 1986). Consequently, there may exist a hyperinnervation of schizophrenic striatum by 5-HT afferents including aberrant innervation to the dorsal caudate.

We also observed a substantial increase in the number of 5-HT_2 receptors in the schizophrenic cases, but the increases were not in the same regions as those for the 5-HT uptake sites. The ventral putamen and nucleus accumbens showed significant increases not observed in the dorsal striatum. The increase in the number of 5-HT_2 receptors was evident with both [^{3}H]ketanserin and with [^{125}I]LSD binding. Moreover, there was no evidence that the affinity of [^{125}I]LSD for 5-HT_2 receptors differed between the control and schizophrenic cases, indicating that there was a better than 1.8-fold increase in the number of receptors in the schizophrenia group. This report differs from previous reports of no difference between schizophrenic and control groups for the number of 5-HT_2 receptors in the caudate-putamen (Owen et al. 1981) or nucleus accumbens (Mackay et al. 1978). Direct comparison of our results with those of previous studies is difficult, as nonselective radioligands were used, and the regions examined may not be comparable to those used in this autoradiographic study. In contrast to our results for 5-HT_2 receptors in the schizophrenic group, no change in the number of 5-HT_{1A} receptors was observed in the striatum. We have previously observed in schizophrenic cases that the dorsal caudate nucleus shows a reduction in the number of DA uptake sites (Joyce et al. 1988) and an increase in the number of β_1 adrenergic receptors (Joyce et al. 1992). The dorsal striatum also evidenced an increase in patches of binding for [^{3}H]CN-IMI binding to 5-HT uptake sites. The ventral striatum displays an increase in 5-HT_2 receptors, 5-HT uptake sites, an increase in DA D2 receptors (Joyce et al. 1988), and β_1-adrenergic receptors (Joyce et al. 1992). The results of this and previous studies (Joyce et al. 1988, 1992) suggest that the compartmental organization of the monoamine systems may be altered in schizophrenic cases. It will be important to determine whether the differences between the schizophrenic and control groups in the striatal organization of the DA system, 5-HT system, and noradrenergic system reflect a generalized disturbance in the boundaries of the striosomal and matrix compartments.

Cortex and Hippocampus

Previous studies have demonstrated that the 5-HT_{1A} receptor represents the major member of the 5-HT_1 family in all cortical regions and in the hippocampus (Dillon et al. 1991; Pazos et al. 1987a). In the cortex, the 5-HT_{1A} receptor shows a different pattern from the 5-HT_2 receptor with the 5-HT_{1A} receptor highest in the external laminae and the 5-HT_2 receptor higher in the internal laminae (Dillon et al. 1991; Lidow et al. 1989; Pazos et al. 1987a, 1987b). Consistent with those data, we found that in most cortical regions the binding of [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors was better than threefold higher in laminae I and II than laminae III–VI. Using [^{125}I]LSD to label 5-HT_2 receptors, we found higher binding in the intermediate laminae (40% to 100% higher numbers) than external or deep laminae of frontal, occipital, parietal, and temporal cortices. This pattern was consistent across cortical regions except for the cingulate cortex, which showed equivalent binding in laminae III and IV, and the motor cortex, which showed a very indistinct laminar organization. We found that [^{3}H]ketanserin binding exhibited a less substantial laminar appearance than [^{125}I]LSD binding, but Beigon and associates (1986) have reported that [^{3}H]ketanserin binding is higher in laminae IV than other laminae of the frontal cortex of humans. Moreover, a recent study by Arango and associates (1990) also indicated that [^{125}I]LSD-labeled sites show the highest binding in the intermediate layers of the frontal cortex. The higher degree of laminar organization observed with [^{125}I]LSD than [^{3}H]ketanserin may reflect differences in the quenching properties of ^{3}H-radioligands as compared to ^{125}I-radioligands in cortex (Lidow et al. 1988).

The pattern of 5-HT_{1A} receptors that were sampled differed in the temporal cortex (superior, middle, and inferior gyri) as compared to the frontal cortex. We determined that the number of 5-HT_{1A} receptors was more than threefold higher in the upper and deep laminae than in the middle laminae (see also, Dillon et al. 1991). Previous reports have also indicated that the entorhinal cortex shows a highly laminated pattern of 5-HT_{1A} receptor expression with layers I–II and V higher than III or VI. We found this also to be the case, although we observed almost similar levels of binding in the deep and upper laminae. We observed that 5-HT_2 receptors labeled with [^{125}I]LSD were significantly lower in number in the entorhinal cortex than

the isocortex or hippocampus. The binding in the entorhinal cortex was denser in laminae III and IV than the other laminae. This contrasts with the region immediately adjacent to the entorhinal cortex, the perirhinal cortex of the lateral occipitotemporal gyrus, which does show significantly higher binding than the entorhinal cortex. Similar findings were found by Gross-Isseroff and associates (1990) using the compound [^{3}H]ketanserin to label 5-HT$_2$ sites.

Our results regarding the distribution of 5-HT$_{1A}$ and 5-HT$_2$ receptors in the hippocampus extend previous findings by directly examining differences in expression between the rostral and the midbody of the hippocampus. It has been reported that in the hippocampus, 5-HT$_{1A}$ receptors were densest over the pyramidal layers of CA$_1$–CA$_2$, low to CA$_3$, and high in the molecular layer of DG (Dillon et al. 1991; Pazos et al. 1987a). We also observed that the CA$_1$ subfield showed the highest binding in the hippocampus and the CA$_2$ subfield appeared lighter than the CA$_1$ subfield in most cases. We did not observe dense binding in the molecular layer of the DG in either the midbody or rostral portion of the hippocampus. The differences in the reported pattern of binding of [^{3}H]8-OH-DPAT to 5-HT$_{1A}$ receptors in the DG with this study and previous studies cannot be attributed to differences in the incubation conditions as similar methodologies were utilized. We determined that the binding of [^{3}H]8-OH-DPAT to 5-HT$_{1A}$ receptors was greatest in the rostral hippocampus and differentiation between subfields was more difficult in this region than in the midbody of the hippocampus. This difficulty in differentiating subfields in the rostral hippocampus might contribute to the variability in the reports. This issue is also relevant to the studies of 5-HT$_2$ receptors in hippocampus which have been reported to be higher in number in the CA$_1$–CA$_3$ subfields and DG than in the subiculum, but significantly lower than the isocortex (Hoyer et al. 1986; Pazos et al. 1987b). We found a more clearly differentiated pattern of expression using [^{125}I]LSD to label 5-HT$_2$ receptors, with differences in the number of 5-HT$_2$ receptors in the rostral as compared to the midbody of the hippocampus. The number of 5-HT$_2$ receptors was found to be quite low for all subfields rostrally, particularly the subiculum and CA$_1$, but reasonably high in the midbody of the hippocampus. In the midbody of the hippocampus, the subiculum and CA$_1$ subfields exhibited the highest number of receptors, and the CA$_3$ and DG the lowest number. The differences between our study and others describing the pattern of 5-HT$_2$ receptors do not appear to reflect different pharmacologic properties of [^{125}I]LSD binding as compared to [^{3}H]ketanserin; our preliminary studies did not indicate [^{125}I]LSD-labeled sites in cortex and hippocampus that [^{3}H]ketanserin did not recognize. There was one exception, in the molecular layer of the DG and moleculare radiatum of the CA$_1$ of the hippocampus, the binding of [^{125}I]LSD was not displaced by ketanserin, and there was no significant [^{3}H]ketanserin binding. However, the nonselective properties of [^{3}H]ketanserin (Hoyer et al. 1987; Leysen et al. 1987, 1988) could contribute to the different findings. Although [^{3}H]ketanserin has been the preferred radioligand for the study of 5-HT$_2$ receptors, it is known to label the monoamine transporter located on synaptic vesicles (Leysen et al. 1987, 1988) and α_1-adrenergic receptors (Hoyer et al. 1987), as well as the 5-HT$_2$ receptor, and may not be the most suitable radioligand for visualizing 5-HT$_2$ receptors. Our findings would argue for an almost complementary organization of 5-HT$_{1A}$ receptors and 5-HT$_2$ receptors in isocortex, particularly in the temporal lobe and in the rostral hippocampus.

Previous reports of the autoradiographic pattern of [^{3}H]imipramine (Gross-Isseroff and Biegon 1988), [^{3}H]desmethylimipramine (Gross-Isseroff et al. 1988), and [^{3}H]paroxetine (Cortés et al. 1988) binding to 5-HT uptake sites in human cortex did not demonstrate a strong laminar pattern and only small differences in density between cortical regions were observed. The pattern of 5-HT uptake sites in cortex labeled with [^{3}H]imipramine was shown to be somewhat denser in the internal as compared to the external laminae in one autoradiography study (Cortés et al. 1988). In contrast, we found that the pattern of binding of [^{3}H]CN-IMI to 5-HT uptake sites was highest in the upper laminae, somewhat lower in the middle laminae, and lowest in the deep laminae. The different results may reflect the binding of [^{3}H]imipramine and [^{3}H]desmethylimipramine to sites not associated with the 5-HT uptake site (D'Amato et al. 1987). However, in the primate cortex, the density of 5-HT immunoreactive fibers was observed to be relatively similar across all laminae with small variations in patterning. In frontal cortex there were slightly higher densities in layer I, but in motor and parietal cortex, the fibers were denser in the supragranular layers (Tork 1990; Wilson and Molliver 1991). Our observations on the pattern of 5-HT uptake sites in the hippocampus, relatively high in the entorhinal cortex and DG, lower in CA$_3$, and lowest in the CA$_1$ subfields of the hippocampus, are consistent with immunocytochemical studies of the patterning of 5-HT axons (Amaral and Campbell 1986; Tork 1990). Our findings are also consistent with the previous autoradiographic studies of the labeling of 5-HT uptake sites with [^{3}H]imipramine by Biegon and associates (Gross-Isseroff and Biegon 1988) but differ from the findings of Cortés and associates (1988). Consequently, the pattern of distribution of [^{3}H]CN-IMI binding to 5-HT uptake sites may not perfectly correlate with the distribution of 5-HT fibers in the cortex but appeared to be highly correlated in the medial temporal lobe (and stri-

atum, see above). The distribution of [^{3}H]CN-IMI binding to the 5-HT uptake sites appeared to match the combined distributions of the 5-HT_{1A} receptor and the 5-HT_2 receptor in the frontal cortex. In the temporal lobe, the superior, middle, and inferior gyri showed a less obvious overlap. In the entorhinal cortex, the pattern of 5-HT_{1A} receptors and 5-HT uptake sites contrasted with the low density of 5-HT_2 receptors. In the hippocampus there was a contrasting pattern of 5-HT uptake sites, 5-HT_{1A} receptors, and 5-HT_2 receptors.

Alterations in Schizophrenia

In contrast to what we found in the striatum, the number of 5-HT uptake sites was not increased in any cortical region of the schizophrenic group. There was, in fact, a marked reduction of sites in the external and middle laminae of the anterior cingulate cortex, frontal cortex, and posterior cingulate cortex but not in the motor cortex, temporal cortex, or hippocampus. One group found reduced numbers of [^{3}H]imipramine sites in the frontal cortex of the right hemisphere of schizophrenics as compared to controls, but no differences for the left hemisphere (Demeter et al. 1989). In a published abstract, Laruelle and associates (1990) reported a reduction in [^{3}H]paroxetine binding to frontal cortex in postmortem brains of schizophrenics. There have been no studies that have reported changes in the levels of 5-HT in the frontal cortex or any other cortical region (Crow et al. 1979; Joseph et al. 1979; Korpi et al. 1986; Winblad et al. 1979). In both previous studies using radioligands to label5-HT uptake sites, it was found that patients with a diagnosis of depression (Demeter et al. 1989) or who had committed suicide (Laruelle et al. 1990) also had reductions in the number of sites that were similar in magnitude to the schizophrenic cases. This raises the possibility that the changes in the number of 5-HT uptake sites found in this study for the anterior cingulate cortex, frontal cortex, parietal cortex, and posterior cingulate cortex cannot be attributed to schizophrenia per se, but would be common to many psychiatric illnesses that have an affective component (Crow et al. 1984; Gross-Isseroff et al. 1989; Stanley et al. 1982; Zubenko et al. 1991). However, other groups have not found any changes in [^{3}H]imipramine (Gross-Isseroff et al. 1989), [^{3}H]desmethylimipramine (Gross-Isseroff et al. 1988), or [^{3}H]paroxetine (Lawrence et al. 1990) binding in suicide cases for brain regions that we determined were altered in the schizophrenia group (striatum, frontal, cortex, or cingulate cortex). Consequently, it will be important to examine the specificity of the changes in 5-HT uptake sites in schizophrenia and other disorders with an affective component in further studies.

In the same schizophrenic group, 5-HT_2 receptors were substantially elevated in the posterior cingulate (middle laminae), temporal cortex (middle laminae), and hippocampus but not altered in the frontal, anterior cingulate, or motor cortices. Previous studies (Arora and Meltzer 1991; Mita et al. 1986) reported finding a decrease in [^{3}H]spiroperidol or [^{3}H]ketanserin binding to 5-HT_2 receptors in the frontal cortex of schizophrenics as compared to controls. They attributed the results to a reduction in the maximum number of 5-HT_2 sites and not to a change in the affinity of the compounds for the 5-HT_2 sites. It is unclear if these discrepant results reflect the utilization of different radioligands, different groups of patients, methods of tissue preparation (membrane binding versus autoradiographic methods), or even region of the brain. The region designated as frontal cortex in this study did not include the frontal pole, which was included in the previous studies. Additionally, there were a number of reports that suicide is related to an elevation in 5-HT_2 receptors in the frontal cortex (Arango et al. 1990; Mann et al. 1986; McKeith et al. 1987; Arora and Meltzer 1989a). Some of our schizophrenic cases had committed suicide, and this may have contributed to variability in the results of 5-HT_2 receptor measurement in frontal cortex.

We found elevations in several regions of the postcentral cortex, including the posterior cingulate (middle laminae), temporal cortex (middle laminae), and hippocampus. However, in the medial temporal lobe the entorhinal cortex was not affected. An examination of 5-HT_2 receptor expression in schizophrenia for regions outside the frontal cortex has not been previously reported. The alterations in 5-HT_2 receptor density that we observed were unlikely to be due to antipsychotic medication, age, or cause of death. Chronic administration of classic antipsychotics, such as haloperidol, has been shown *not* to modify (O'Dell et al. 1990; Wilmot and Szczepanik 1989), or even decrease (Lee and Tang 1984; Andree et al. 1986), the number of 5-HT_2 receptors in frontal cortex of rats. In fact, increases in the density of 5-HT_2 receptors could not be induced by any method that reduced 5-HT transmission or with chronic treatment with antidepressant drugs (for review, Frazer et al. 1988). Gross-Isseroff and associates (1990) have reported that 5-HT_2 receptor density was affected somewhat by age, but in a region specific manner. Receptor number was decreased in the frontal cortex and hippocampus and not other cortical or subcortical regions of elderly as compared to young patients. Since the group of schizophrenics that were utilized in this study contained a number of cases that were younger than the control cases and had committed suicide, there was the potential concern that the observed changes might be related to age. Additionally, there were a number of reports that suicide is related to an elevation in 5-HT_2 receptors in the frontal cortex (Arango et al. 1990; Mann et al. 1986; McKeith et al. 1987; Arora and Meltzer 1989a). Therefore, we exam-

ined the 5-HT system in the parietal cortex and temporal cortex of a group of cases that had committed suicide, did not have a diagnosis of schizophrenia, and were of a younger age than the control group. Some differences from controls were apparent, but these were not regionally the same as found in the schizophrenic group. No change in the pattern or number of 5-HT_2 sites was observed in the temporal cortex (or hippocampus) of suicide cases as compared to controls. This latter finding was in agreement with the recent autoradiographic study by Arango and associates (1990) that found increases in 5-HT_2 receptors in the frontal cortex, but not the temporal cortex of suicide cases.

We observed increased numbers of 5-HT_{1A} receptors in those brain regions of schizophrenics that did not show changes in the number of 5-HT uptake sites, including the posterior cingulate and the motor cortex. We also observed increased numbers of 5-HT_{1A} receptors in the hippocampus, but not the entorhinal cortex. For several reasons, we believe these changes in 5-HT_{1A} receptors in the hippocampus to be disease specific. First, there was no significant overlap of the regions showing increases in 5-HT_{1A} and 5-HT_2 receptor numbers; thus, there is regional selectivity in the receptor alterations in schizophrenia. Second, although the increase in number of 5-HT_{1A} receptors in the hippocampus of the schizophrenics was also observed in the suicide cases, the subfields affected were not the same in the schizophrenic and suicide cases. The increase in 5-HT_{1A} receptors was significant for the DG of the schizophrenic group and for the CA_1–CA_3 subfields of the suicide group. Biegon and associates (Dillon et al. 1991) have also explored whether 5-HT_{1A} receptor number was altered in suicide cases. Although they observed a tendency for an increase in number in the hippocampus, the only significant findings related to those cases were that ethanol consumption was high. Consequently, the changes in 5-HT_{1A} receptor numbers associated with schizophrenia are likely to be different from suicide processes. In contrast to other regions of the brain, 5-HT_{1A} receptors in the hippocampus could be modified by lesions to the 5-HT system and by chronic administration of some antidepressant drugs (Hensler et al. 1991). Serotonin$_{1A}$ receptors are thought to be located on cells postsynaptic to the terminals in cortical regions and in the hippocampus (Gozlan et al. 1983; Hall et al. 1985). Administration of tranylcypromine, but not other antidepressant drugs, can increase the number of receptors in the CA_2–CA_3 subfields of the hippocampus but not in cortical regions (Hensler et al. 1991). Whereas some patients in the suicide group had taken antidepressants, there was no evidence that the schizophrenic patients were taking antidepressants or alcohol. Additionally, we did not find a reduction in 5-HT uptake sites in the regions of the cortex and hippocampus where elevations in 5-HT_{1A} receptors were found. Consequently, the increase in 5-HT_{1A} receptors in the DG of the schizophrenic cases was unlikely to be due to drug treatment, response to reduced 5-HT, or inclusion of schizophrenic cases that committed suicide. However, caution must be used in interpreting these findings; Winblad and associates (1979) have found a reduced 5-HT content in hippocampus of schizophrenic cases. One group has also recently reported that an increase in 5-HT_{1A} receptor number could be found in the prefrontal cortex and temporal lobe but not in the hippocampus of elderly schizophrenic cases (Hashimoto et al. 1991). The study utilized membranes derived from these regions of brain and so may not be directly comparable to our study. Our data show that 5-HT_{1A} receptors were affected differently from 5-HT_2 receptors in the schizophrenic group and support the view that the elevation in 5-HT receptors in a number of cortical regions was an important finding.

SUMMARY

Our results suggest that in schizophrenia, there are selective changes in the 5-HT system in structures that compose the limbic system including the cortex, hippocampus, and striatum. These data support the hypothesis that the 5-HT system plays a role in schizophrenia (Bleich et al. 1988; Meltzer 1989). Our results show that more than one component of the 5-HT systems is directly altered in schizophrenia, with increased 5-HT receptor number in several limbic regions. A supersensitive 5-HT system in schizophrenia is suggested by the evidence that compounds with antiserotonergic properties have antipsychotic properties (Castelaoo et al. 1989; Meltzer et al. 1989; Vinar et al. 1989). More recently, Iqbal and associates (1991) examined the response of schizophrenic patients to direct challenge with a 5-HT agonist and found marked worsening of symptoms, also suggestive of a supersensitive 5-HT system. Chronic treatment with many of the atypical antipsychotics can reduce the number of 5-HT_2 receptors (Leysen et al. 1987b; O'Dell et al. 1990; Wilmot and Szczepanik 1989). It will be important to determine if modification of receptor number in limbic cortex and limbic regions of striatum may be a means by which these drugs can interfere in the development of psychotic symptoms.

ACKNOWLEDGMENTS

This research was supported by U.S. Public Health Service Grants MH 43852 and MH 43880, AG 09215 to J.N. Joyce; Research Scientist Award MH 00044, R01NS 19597, and DRSG2-S07-PR-05415-26 to A. Winokur; and National Institutes of Health Grant MH 31862 to Dr. Bird (McLean Hospital, Belmont, MA) for the Brain Tissue Resource Center.

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