J Neural Transm [GenSect] (1991) 85: 181–194

Journal of Neural Transmission

© Springer-Verlag 1991
Printed in Austria

Serotonergic measures in suicide brain: 5-HT_{1A} binding sites in frontal cortex of suicide victims

S. Matsubara[1], **R. C. Arora**[2], and **H. Y. Meltzer**[2]

[1] Department of Psychiatry, Hokkaido University School of Medicine, Hokkaido, Japan
[2] Laboratory of Biological Psychiatry, Department of Psychiatry, Case Western Reserve University, School of Medicine, Cleveland, Ohio, U.S.A.

Accepted March 8, 1991

Summary. The density of 5-HT_{1A} binding using ^{3}H-8-hydroxy-2-(di-n-propyl-amino) tetralin (8-OH-DPAT) as binding ligand, was studied in human frontal cortex of suicide victims and normal controls who died due to medical disease or accidentally. There was no difference in the maximum number of binding site (B_{max}) or K_d (an inverse measure of affinity) of 5-HT_{1A} receptor binding sites between normal controls and the entire group of suicide victims. However, nonviolent suicides had significantly higher B_{max} (22–25%) compared to both controls and violent suicides. A negative correlation between age and B_{max} of 5-HT_{1A} binding sites was found in male controls but not in female controls or suicide victims. This relationship was less apparent among the male controls over age 60.

Keywords: Serotonin$_{1A}$ (5-HT_{1A}) receptor, brain, suicide.

Introduction

It has been suggested that there is an association between disturbances in brain serotonin (5-HT) metabolism, suicidal and violent behavior. Lower levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, in cerebrospinal fluid (CSF), have been found in both depressed and nondepressed patients who made violent suicide attempts compared to those whot did not (Asberg et al., 1976; Agren, 1980; van Praag, 1983; Banki and Arato, 1983). Reduced CSF 5-HIAA levels has also been found to be associated with high level of aggressive behavior towards self and others (Asberg et al., 1980, 1987), personality disorders with impulsive violent behavior (Brown et al., 1979) and high levels of anxiety and agitation in depressed patients (Banki, 1977; Asberg et al., 1980; Leckman et al., 1980).

Post-mortem studies of the brains of suicide completers have sometimes

produced results consistent with an abnormality of 5-HT. Decreased levels of 5-HT and/or 5-HIAA have been reported in the brainstem of suicide victims by some investigators (Shaw et al., 1967; Pare et al., 1969; Lloyd et al., 1974), whereas no differences (Beskow et al., 1976; Cochran et al., 1976; Stanley et al., 1983; Owen et al., 1983; Crow et al., 1984; Arato et al., 1987; Cheetham et al., 1989; Ohmori and Meltzer, in preparation) or even increases have also been reported in various areas of the brain (Owen et al., 1986; Cheetham et al., 1989).

Recent studies of the serotonergic system in suicide have focused on brain 5-HT binding sites. 5-HT binding sites in the central nervous system have been classified by means of radioligand binding studies into three major classes: 5-HT_1, 5-HT_2 and 5-HT_3 (Peroutka et al., 1988). Recently, Stanley and Mann (1983) and Mann et al. (1986) reported an increase in the number of 5-HT_2 receptor binding sites in human frontal cortices of suicide victims. Cheetham et al. (1988) did not find any difference in 5-HT_2 binding between depressive suicide victims and normal controls. However, they found a tendency towards an increased binding (B_{max}) in the frontal cortex of suicide victims who died by violent means. We also reported an increase in 5-HT_2 receptor density (B_{max}) in frontal cortices of suicide victims; the increase was more pronounced in suicides who used violent means, i.e., gunshot wound or hanging, than non-violent suicides (Arora and Meltzer, 1989). McKeith et al. (1987) reported a nonsignificant increase in 5-HT_1 and 5-HT_2 binding in the frontal cortex of patients with major affective disorders compared to normal controls. On the other hand, several authors reported no difference in 5-HT_1 receptors between suicides and controls (Owen et al., 1983, 1986; Crow et al., 1984; Mann et al., 1986).

Because the 5-HT_1 binding in human cortex is heterogeneous, e.g., 5-HT_{1A}, 5-HT_{1C} and 5-HT_{1D} (Todd and Ciaranello, 1987; Peroutka, 1988) it is important to investigate whether the binding of one or more of the 5-HT_1 subtypes differs in suicides. We were particularly interested in the 5-HT_{1A} receptors which are associated with anxiety and depression (McMillan et al., 1987; Kennett et al., 1987). We have now determined 5-HT_{1A} binding in the frontal cortex of violent and nonviolent suicides and compared with the age- and sex-matched controls who died from medical diseases or accidentally.

Methods

Subjects

Frontal cortex samples (Broadmann's areas 8 and 9) from suicide victims and controls were obtained at autopsy at Cuyahoga Coroner's Office, Cleveland, Ohio 44106. The samples were stored at −80 °C until used. The controls consisted of brain specimens from people who died of coronary heart disease (n = 23), accidents (n = 7) or homicides (n = 10). There were 18 female and 22 male controls, 11 female and 12 male suicides. The mean (± S.D.) age of the controls and suicides was not significantly different (Tables 1, 2).

The medical examiner's office determined the cause of death in suicides and controls. The sex, age, post-mortem delay, cause of death, as well as B_{max} and K_d sites in frontal cortex, are given in Tables 1 and 2 for the controls and suicides.

Table 1. Demographic data, cause of death and 5-HT_{1A} binding data in controls

Sex	Age	P-M delay (hr)	Cause of death	B_{max} (pmol/g)	K_d (nM)
M	21	5.0	H GSW	5.05	0.67
M	70	8.0	N CHD	2.86	0.55
*M	54	26.0	N bronchopneumonia	8.22	0.92
F	26	3.0	H GSW, STW	3.41	1.32
M	54	7.0	N CHD	4.71	1.17
M	63	6.0	H GSW	4.23	0.77
F	52	7.0	N pulmonary thromboemboli	3.52	0.69
F	25	5.0	A MVA	5.78	0.51
F	69	14.0	N CHD	3.84	0.47
F	72	20.0	A MVA	4.58	0.54
M	62	17.0	N CHD	5.24	0.66
F	39	5.0	N cardiomyopathy	4.86	0.54
M	65	12.0	N CHD	4.37	0.73
M	25	32.0	C pulmmonary thromboemboli	4.28	1.34
M	32	13.0	N CHD	6.23	0.95
F	45	10.0	N CHD	3.85	1.05
F	83	17.0	A MVA	5.17	0.60
M	37	19.0	N CHD	4.57	0.80
F	53	14.0	N hypertensive cardiovascular disease	5.61	0.94
M	75	20.0	N CHD	3.99	0.52
F	29	17.0	H GSW	4.35	0.59
M	69	37.0	N CHD	4.17	0.66
F	43	13.0	N gastric haemorrhage	3.98	0.63
M	39	16.0	N CHD	4.96	0.67
M	35	6.0	N CHD	5.43	0.93
M	65	7.0	N CHD	3.83	0.47
F	31	16.0	H GSW	5.46	0.78
M	27	16.0	H GSW	3.87	0.40
M	31	6.0	H GSW	6.26	0.65
M	33	9.0	H GSW	5.08	0.70
M	63	12.0	A burns	4.12	0.54
F	37	10.0	A hypothermia	4.60	0.55
M	56	3.0	N thromnboemboli	4.02	0.43
F	55	9.6	N cardiomyopathy	4.41	0.44
F	72	13.8	N CHD	3.52	0.49
F	69	8.0	A thromboemboli	5.19	0.87
F	35	30.3	A therapeutic complication	4.33	0.59
M	25	8.9	H GSW	4.67	0.53
M	61	7.0	H GSW	3.25	0.60
F	37	20.8	N CHD	3.57	0.44
Mean:	48.2 ± 17.8	12.6 ± 7.8		4.49 ± 0.80	0.69 ± 0.23

H homicide; *A* accident; *N* natural death; *GSW* gunshot wound; *STW* stab wound; *MVA* motor vehicle accident; *CHD* coronary heart disease

Table 2. Demographic data, cause of death, and 5-HT_{1A} binding data in suicides

Sex	Age	P-M delay (hr)	Cause of death*	B_{max} (pmol/g)	K_d (nM)
Non-violent suicides					
M	24	13.0	CO	4.11	0.86
M	21	4.0	CO	6.91	0.76
F	62	15.0	OD	6.40	0.72
F	87	19.0	OD	4.88	1.32
M	27	3.0	CO	6.91	0.66
M	43	9.0	CO	6.72	1.11
M	37	5.0	OD	5.73	0.59
M	33	13.0	OD, pneumonia	7.46	0.65
F	52	23.0	CO	2.64	0.63
F	62	6.0	OD	3.37	0.57
F	48	24.0	CO	5.18	0.61
F	50	17.0	OD	5.42	1.14
Mean	45.5 ± 19.0	12.5 ± 7.29		5.48 ± 1.52	0.80 ± 0.25
Violent suicides					
M	57	10.0	GSW	4.17	0.58
M	27	23.0	GSW	3.79	0.55
M	72	21.0	hanging	3.40	0.82
M	85	17.0	hanging	6.98	0.70
M	28	20.0	hanging	4.57	0.81
F	58	24.0	STW	3.40	0.68
M	25	9.0	hanging	4.87	0.60
F	33	2.1	GSW	4.43	0.44
F	63	21.8	jumping	5.07	0.49
F	67	15.0	hanging	3.64	0.48
F	55	24.0	GSW	3.81	0.58
Mean	48.5 ± 19.5	17.0 ± 7.2		4.38 ± 1.03	0.62 ± 0.14

CO carbon monoxide poisoning; *OD* overdose

The storage time for the controls brains was 371 ± S.D. 157 days; for the violent and nonviolent suicides, it was 327 ± S.D. 164 and 333 ± S.D. 127 days, respectively.

None of the controls or suicide victims had any psychoactive drugs as determined by blood toxicology studies.

Assays

Gray matter was dissected on ice from each tissue block, dura mater was removed, excessive water was blotted, and the grey matter weighed. Pairs of samples from a control and suicide

were usually assayed blindly. Whereever possible, we matched controls and suicides by cause of death, age, sex and post-mortem delay.

Tissues were homogenized with Polytron (setting 6, 20 sec.) in 50 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.7 at 25 °C) containing 5 mM EDTA. The homogenates were centrifuged at 48,000 × g for 10 min at 4 °C. The pellets were washed with the same buffer and centrifuged again. The pellets were resuspended in 50 mM Tris-HCl buffer (pH 7.7 at 25 °C) and incubated for 10 min at 37 °C, cooled, and then centrifuged. The final pellets were resuspended in this buffer prior to use in the binding assay.

[^{3}H]8-hydroxy-2-(di-n-propylamino)tetralin ([^{3}H]8-OH-DPAT) (160–201 Ci/mmol, Amersham) and [^{3}H]5-HT (26 mCi/mmol, NEN) were used to label 5-HT_{1A} and 5-HT_1 receptors, respectively, according to the method of Peroutka (1986). [^{3}H]8-OH-DPAT or [^{3}H]5-HT was incubated at 25 °C for 30 min in 50 mM Tris-HCl buffer (pH 7.7) containing 0.1% ascorbate, 4 mM $CaCl_2$, 10 μM pargyline with an aliquot of the membrane (7 mg original wet weight) either in the presence or absence of 10 μM 5-HT. Six concentrations of [^{3}H]8-OH-DPAT (0.05–5 nM) were used for binding assays. Incubations were terminated by rapid filtration under reduced pressure over Whatman GF/C filter. The filters were rinsed three times with 5 ml of ice cold 50 mM Tris-HCl buffer (pH 7.7 at 25 °C), then transferred to counting vials containing 9 ml of Safety-Solve® (Research Product International Corporation, IL), and counted by liquid scintillation spectrometry after overnight extraction (efficiency = 43%). All assays were done in duplicate.

Scatchard analysis was performed to determine the apparent dissociation constant (K_d) and the density (B_{max}) of specific binding sites. Inter-assay variance (S.D./mean × 100 of [^{3}H]8-OH-DPAT bindings were determined by three independent experiments: 9.4 percent for B_{max} and 9.5 percent for K_d. In the strict sense, these were not interassay variances, because the site of dissection of gray matter from the brain block could not be the same in each experiment. Intra-assay variance of [^{3}H]8-OH-DPAT specific bindings at three different concentrations of the ligand was less than 2.2 percent.

Association studies were performed by incubating normal frontal cortex membrane (5–7 mg, wet weight) with [^{3}H]8-OH-DPAT (1 nM) with and without the addition of 5-HT (10 μM). The incubations were done for various length of times 5–45 min and processed as described above. Association was complete in 20 min and the binding remained constant thereafter. Hence, the incubations were performed for 30 min (data not presented).

All results are mean ± S.D. The Pearson correlation coefficient was calculated for all variables which were normally distributed. The post-hoc test (ANCOVA analyses) of least-square means were done using the least significant difference approach (Kirk, 1982) for pairwise comparisons.

Results

Existence of 5-HT_{1A} receptor subtype in human frontal cortex

In order to characterize 5-HT_1 specific binding in human frontal cortex, we studied the effect of spiperone which binds to 5-HT_2 receptor and 8-OH-DPAT which binds to 5-HT_{1A} receptor on ^{3}H-5-HT binding in rat brain. Both drugs inhibit 5-HT binding in biphasic manner, suggesting that total 5-HT_1 specific binding sites consists of at least two sites, one of which has high affinity for 8-OH-DPAT and spiperone. In the present study, we studied 5-HT_{1A} receptor binding using [^{3}H]8-OH-DPAT as binding ligand.

[^{3}H]8-OH-DPAT binding to human frontal cortex membranes was saturable and had high affinity. Scatchard transformation of the saturation data resulted in a linear plot which confirms the existence of a single population of

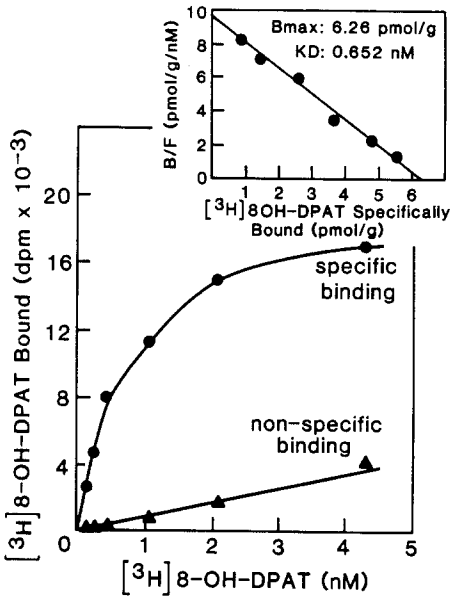

Fig. 1. [^{3}H]8-OH-DPAT binding as a function of increasing concentrations of [^{3}H]-OH-DPAT in the frontal cortex of normal control. Upper panel is a Scatchard plot

binding sites in these membranes (Fig. 1). B_{max} and K_d values of the binding sites in normal controls were 4.49 ± 0.80 pmol/g tissue and 0.69 ± 0.23 nM, respectively.

B_{max} of "total" 5-HT_1 receptor binding sites calculated from [^{3}H]5-HT saturation experiments in frontal cortex from three normal controls was 12.56 ± 0.86 pmol/g. B_{max} of [^{3}H]5-HT binding in the present of 30 nM 8-OH-DPAT, which masks the 5-HT_{1A} component, was 9.09 ± 1.00 pmol/g. The difference in B_{max} values for the two methods was 3.47 ± 0.96 pmol/g which is similar to the B_{max} obtained from [^{3}H]8-OH-DPAT saturation studies in 39 normal controls (4.72 ± 1.16 pmol/g). The B_{max} and K_d values of one control subject (marked with an asterisk in Table 1) were omitted because this B_{max} value, 8.22 pmol/g, was greater than the mean + 3 S.D. for the entire control group. K_d for the ^{3}H-5-HT binding site without 8-OH-DPAT was 1.87 ± 0.87 nM and 2.15 ± 0.74 nM. These are not significantly different. There was also no difference in K_d or B_{max} between homicides and other control groups, i.e., coronary heart disease and accident victims. Hence, they were combined together and referred to as normal controls in other comparisons.

Effect of autopsy delay and duration of storage

The time between death and autopsy did not correlate with 5-HT_{1A} receptor parameters (B_{max}, K_d); however, there was a positive correlation between duration of storage and K_d value: (Pearson, r = 0.31, m = 62, p = 0.01) but not

Table 3. B_{max} and K_d of 5-HT_{1A} binding sites in frontal cortex of controls and suicides

Group	N	B_{max} (pmols/gm)	K_d (nM)
Controls	39	4.50 ± 0.80	0.69 ± 0.23
Suicides	23	4.95 ± 1.40	0.71 ± 0.22

B_{max}. Therefore, in subsequent analyses, data were analyzed by analysis of variance (ANOVA) after covarying K_d and other variables.

Age and sex influence

We studied the effect of age and sex on 5-HT_{1A} receptors as determined by [^{3}H]8-OD-DPAT binding in the human frontal cortex. There were no significant sex differences between B_{max} and K_d for either the control group or the suicides (Table 3). There was a significant partial correlation between age and B_{max} controlling for storage time ($r = 0.32$, $n = 39$, $p = 0.049$) in the control group but not the suicides (data not presented). However, when female and male controls were analyzed separately, the correlation between age and B_{max} was significant in the males ($r = -0.58$, $n = 21$, $p = 0.008$) but not in the females ($r = 0.010$, $n = 18$, $p = 0.968$, Fig. 2). This negative correlation and group difference remained even with inclusion of the data from the omitted subject. K_d and age were not significantly correlated for the controls. B_{max} and K_d were not significantly correlated with age in the suicides for males alone, females alone, or the combined group (data not presented).

Suicides vs. non-suicides

Analysis of variance (ANOVA) examining the effect of sex, race, age, postmortem delay and storage time indicated no difference in B_{max} or K_d of ^{3}H-8-OH-DPAT binding between normal controls and suicides (Table 3). However, when the suicide group was subdivided into nonviolent (i.e., overdose or CO poisoning) and violent suicides (i.e., gunshot wound, stab wound, hanging or jumping from height), nonviolent suicides had significantly higher B_{max} values compared to controls (Table 4, ANOVA, $F = 2.31$, $p < 0.039$). The least square mean values of B_{max} adjusted for sex, race, age postmortem delay and storage time were 4.47 ± S.E. 0.17; 4.44 ± S.E. 0.33, 5.44 ± S.E. 0.33 for normals, violent suicide and non-violent suicides, respectively. The B_{max} of nonviolent suicides was significantly greater than that of the normal controls ($p = 0.007$) and the violent suicides ($p = 0.025$) after controlling for age, sex, race and post mortem delay. This is also true when the B_{max} value of the omitted control subject is included in the analysis. The violent suicides and controls did not differ in B_{max}. There was no differences in K_d values among the three groups.

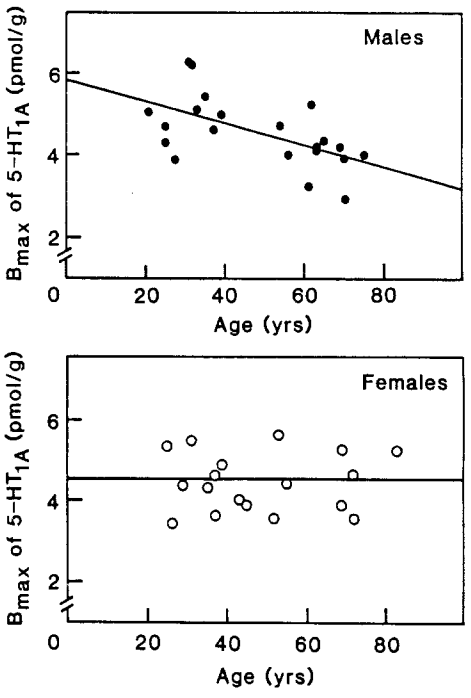

Fig. 2. Correlation between age and B_{max} of 5-HT_{1A} receptors in males and females

Discussion

The major finding in this study was that the number of 5-HT_{1A} binding sites as measured by ^{3}H-8-OH-DPAT binding were increased in nonviolent suicides compared to violent suicides and controls. There was no significant difference in B_{max} between violent suicides and the controls. Before discussing these results, we will consider methodological issues that could affect the interpretation of these findings.

Table 4. B_{max} and K_d of 5-HT_{1A} binding sites in frontal cortex of male and female controls and suicides

Group	B_{max} (pmol/gm)		K_d (nM)	
	Males	Females	Males	Females
Controls	4.54 ± 0.84 (21)*	4.45 ± 0.77 (18)	0.70 ± 0.23 (21)	0.67 ± 0.24 (18)
Suicides	5.47 ± 1.47 (12)	4.39 ± 1.11 (11)	0.73 ± 0.16 (12)	0.69 ± 0.28 (11)
Violent	4.63 ± 1.27 (6)	4.07 ± 0.68 (5)	0.69 ± 0.13 (6)	0.53 ± 0.10 (5)
Nonviolent	6.31 ± 1.22 (6)	4.65 ± 1.39 (6)	0.77 ± 0.19 (6)	0.83 ± 0.32 (6)

* (N)

As has been demonstrated in rat brain (Pedigo et al., 1981; Peroutka, 1986), spiperone or 8-OH-DPAT inhibition of [^{3}H]5-HT binding in human frontal cortex was distinctly biphasic which suggests the presence of at least two different 5-HT_1 receptor subtypes in this region of the human brain. By definition, the component with high affinity not only for 5-HT but also for spiperone and 8-OH-DPAT is a 5-HT_{1A} receptor subtype. In addition, we found that the rank order of affinity of several agents for the [^{3}H]8-OH-DPAT specific binding site was 5-HT > spiperone > mianserin > ketanserin and that the pKi values for each of these agents was in good agreement with that reporte by Hoyer et al. (1986, data not shown). These results suggest that ^{3}H-8-OH-DPAT is binding to a 5-HT_{1A} binding site in human brain.

We found a negative correlation between age and B_{max} of 5-HT_{1A} receptors in male normal controls only (Fig. 2). Middlemiss et al. (1986) also reported a significant negative correlation between age and B_{max} of [^{3}H]8-OH-DPAT binding in normal human temporal cortex but not in frontal cortex. They did not, however, report the sex of normal controls used in the study. The effect of aging on 5-HT_{1A} receptor binding sites in females may be counteracted by changes of hormonal environment (i.e., reduction of ovarian steroid levels) after menopause. We found no evidence that the decrease in B_{max} with age in male controls could be due to the difference in the cause of death or drug effects. Allen et al. (1983) and Marcusson et al. (1984) also found a decrease in the number of 5-HT_1 receptor with age in human cerebral cortex, whereas Bennett et al. (1979) did not. Neither Allen et al. (1983) nor Marcusson et al. (1984) examined sex-age interaction. These studies, however, examined total 5-HT receptor binding whereas we determined only 5-HT_{1A} receptor binding. The age-sex interaction on 5-HT_{1A} sites needs to be replicated in a subsequent study.

Schoemaker and Langer (1986) reported that [^{3}H]8-OH-DPAT labels the 5-HT transporter in rat striatum. Most of the [^{3}H]8-OH-DPAT binding sites in human frontal cortex detected in this assay appear to be receptor binding sites, and not the 5-HT transporter sites, because of the following reasons: 1) Scatchard plot of [^{3}H]8-OH-DPAT binding indicates a single class of binding sites; 2) the K_d value of [^{3}H]8-OH-DPAT for the 5-HT transporter site was reported to be 13.0 nM (Schoemaker and Langer, 1986), which is about 19 times larger than our K_d value (0.69 nM); 3) the concentration of [^{3}H]8-OH-DPAT used in our assay ranged from 0.1 to 5.0 nM. At these concentrations it should be impossible to label low affinity 5-HT transporter sites; 4) Hall et al. (1985) reported that the displacement curves of drugs for the [^{3}H]8-OH-DPAT site in cortical membrane were biphasic and that there was a statistically significant correlation between IC_{50} value of drugs at striatal binding sites and the low affinity component of cortical binding sites. This is not the case in human frontal cortex membranes. Displacement curves of all the drugs tested (5-HT, 8-OH-DPAT, (-)propranolol, spiperone, mianserin and ketanserin) were monophasic. The apparent Hill coefficients were around unity except for spi-

perone (nM = 0.761), which suggests that [^{3}H]8-OH-DPAT labels homogenous binding sites under assay condition (unpublished observations).

As noted previously, B_{max} in nonviolent suicides was significantly increased compared to normal controls and violent suicides. There was no difference in B_{max} or K_d values in the violent suicides compared to the normal controls (Table 4). Several authors have reported that there was no difference in [^{3}H]5-HT binding (5-HT_1 receptors) between suicides and normal controls (Owen et al., 1983, 1986; Crow et al., 1984; Mann et al., 1986), or a slight but nonsignificant increase (McKeith et al., 1987). However, these studies measured "total" 5-HT_1 binding which consist of at least two 5-HT subtypes in human frontal cortex. Because the 5-HT_{1A} receptor subtype accounts for only about 35% of "total" 5-HT_1 binding sites, the effect noted here may not be large enough to be detected by [^{3}H]5-HT receptor binding methods. Further, these studies did not specifically separate nonviolent and violent suicides.

We considered the possibility that upregulation of 5-HT_{1A} receptors could be related to the cause of death, i.e., carbon monoxide poisoning or overdose. Shih and Ohsawa (1983) and Heron et al. (1980) have reported that 5-HT receptors are upregulated in association with increased membrane fluidity in rat and mouse brain, respectively. It is tempting to speculate that carbon monoxide poisoning increases membrane fluidity, resulting in an increased 5-HT_1 binding in nonviolent suicide victims. Additional studies are required to determine membrane fluidity and its relation to 5-HT_1 binding sites in human brain. Subchronic treatment with imipramine (10 mg/kg, i.p., twice a day for 14 days) did not change the 5-HT_{1A} receptor number in rat cerebral cortex (unpublished observation). Repeated treatment of rats with monoamine oxidase inhibitors was reported to downregulate 5-HT_{1A} receptor number (Palfreyman et al., 1987). Accordingly, although it is likely that all of the drugs used to commit suicide produce respiratory depression and hypoxia, it is unlikely that these agents, which are chemically distinct from each other [benzodiazepine, barbiturates, antidepressant (doxepine), neuroleptics (thioridazine) or analgesics], produce a net upregulation of 5-HT_{1A} receptor binding sites. Nevertheless, further study is needed to determine the contribution of co-poisoning and drug effects to the results reported here.

A second possibility to explain the increase in 5-HT_{1A} sites in nonviolent suicides is as a response to diminished serotonergic activity. Some post-mortem studies have found reduced 5-HT or 5-HIAA concentrations in the brainstem of suicide victims (see Introduction). There was, however, no decrease in 5-HIAA levels in the nonviolent suicides compared to violent suicides and normal controls and there was no correlation between B_{max} of 5-HT_{1A} and 5-HIAA concentration in frontal cortex (Ohmori and Meltzer, in preparation). This was also true for 5-HT_2 receptors in frontal cortex and 5-HIAA concentrations (Arora and Meltzer, 1989). The K_d and B_{max} of 5-HT_{1A} and 5-HT_2 receptors were also not correlated in normal or suicide victims. However, we did find a significant negative correlation between brain tryptophan and the B_{max} of 5-

HT_{1A} receptors in the nonviolent suicides (rho = −0.69, N = 11, p = 0.019). A similar trend was present in violent suicides (rho = −0.55, N = 10, p = 0.10) but not in 30 non-suicide controls (Ohmori and Meltzer, in preparation). Tryptophan may be a better indicator of serotonergic activity than 5-HIAA concentration which may reflect intraneuronal catabolism (Woolf et al., 1985). This suggests the possibility that the upregulation of 5-HT_{1A} binding sites in nonviolent suicides might be due to decreased synaptic 5-HT concentrations since tryptophan is the rate limiting step in 5-HT synthesis (Fernstrom and Wurtman, 1971). However, in animal experiments, chemical destruction of 5-HT neurons or repeated reserpine treatment did not change the number of 5-HT_{1A} receptors in rat cerebral cortex (Hall et al., 1985).

The significance of the increase in density of 5-HT_{1A} receptors is difficult to predict at the current time. There is some evidence that drugs which have some specificity for the 5-HT_{1A} receptor have antidepressant properties in man (Goldberg and Finnerty, 1979; Schweizer et al., 1986) or in animals models of depression (Kennett et al., 1987). It is of particular interest that buspirone and gepirone, two drugs with some 5-HT_{1A} spcificity, have antiaggressive effects (McMillen et al., 1987). However, the 5-HT_{1A} binding sites are located both presynaptically on the cell bodies and/or dendrites of serotonergic neurons with the nucleus raphé dorsals and postsynaptically on serotonergic neurons, as evidenced by the decrease and no change in [^{3}H]8-OH-DPAT binding in the dorsal raphé nucleus and frontal cortex or in any other areas of brain, respectively, following selective degeneration of serotonergic terminals and fibers by intracerebral administration of 5-7-dihydroxytryptamine (Hall et al., 1985; Verge et al., 1985, 1986). Thus, the stimulation of 5-HT_{1A} receptors exert complex effects on 5-HT neurotransmission. Stimulation of pre-synaptic 5-HT_{1A} receptors might lead to decreased firing of 5-HT neurons (DeMontigny et al., 1984; Sprouse and Aghajanian, 1986), and diminished release of 5-HT (Goodwin et al., 1986), wherease stimulation of post-synaptic 5-HT_{1A} receptors might lead to enhanced serotonergic activity. Thus, it is difficult to predict what are the functional consequences of 5-HT_{1A} upregulation until it is possible to determine which 5-HT_{1A} sites are increased, functional importance, and numerous other modulating influences. Nevertheless, these results, together with increased 5-HT_2 binding in violent suicides (Mann et al., 1986; Arora and Meltzer, 1989), point to the importance of the violent/nonviolent subtyping of suicide for further research.

Acknowledgements

The research reported was supported in part by USPHS MH 41684, MH 41594, GCRC MO 1RR00080, the Department of Veterans Affairs and grants from the Cleveland, John Pascal Sawyer Memorial and Elizabeth Severance Prentiss Foundations. H. Y. M. is the recipient of a USPHS Research Career Scientist Award MH 47808. We are grateful to Ms. L. Kregel was of great help in collecting the specimens and other information and Ms. L. Mason for secretarial assistance.

References

Agren H (1980) Symptom patterns in unipolar and bipolar depression correlating with monoamine metabolism in the cerebrospinal fluid. II. Suicide. Psychiatry Res 3: 225–236

Allen SJ, Benton JS, Goodhardt MJ, Haan EA, Sims NR, Smith CCT, Spillane JA, Bowen DM, Davison AN (1983) Biochemical evidence of selective nerve cell changes in the normal aging human and rat brain. J Neurochem 41: 256–265

Arato M, Tekes K, Tothfalusi L, Magyar K, Palkovits M, Demeter, Falus A (1987) Serotonergic split brain and suicide. Psychiatry Res 21: 355–356

Arora RC, Meltzer HY (1989) Serotonergic measures in the brains of suicide victims: 5-HT_2 binding sites in the frontal cortex of suicide victims and control subjects. Am J Psychiatry 146: 730–736

Asberg M, Träskman L, Thorén P (1976) 5-HIAA in the cerebrospinal fluid. Arch Gen Psychiatry 38: 1193–1197

Asberg M, Bertilsson L, Rydin E, Shalling D, Thorén P, Träskman-Bendz L (1980) Monoamine metabolism in cerebrospinal fluid in relation to depressive illness, suicidal behavior and personality. In: Angrist B, Burrows GD, Lader M, Lingjaerde O, Sedvall G, Wheatley D (eds) Recent advances in neuropsychopharmacology. Pergamon Press, New York, pp 257–271

Asberg M, Schalling D, Träskman-Bendz L, Wagner A (1987) Psychobiology of suicide, impulsivity, and related phenomena. In: Meltzer HY (ed) Psychopharmacology. The third generation of progress. Raven Press, New York, pp 655–668

Banki CM, Arato M (1983) Amine metabolism and neuroendocrine responses related to depression and suicide. J Affect Dis 5: 223–232

Banki CM (1977) Correlations between anxiety and related symptoms with cerebrospinal fluid 5-hydroxyindoleacetic acid in depressed women. J Neural Transm 41: 135–143

Bennett JP Jr, Enna SJ, Bylund DB, Gillin JC, Wyatt RJ, Snyder SH (1979) Neurotransmitter receptors in frontal cortex of schizophrenics. Arch Gen Psychiatry 36: 927–934

Beskow J, Gottfries CG, Ross B-E, Winblad B (1976) Determination of monoamine and monoamine metabolites in the human brain. Acta Psychiatr Scand 53: 7–20

Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF (1979) Aggression in human correlates with cerebrospinal fluid amine metabolites. Psychiatry Res 1: 131–139

Cheetham SC, Cromptom MR, Katona CLE, Horton RW (1988) Brain 5-HT_2 receptor binding sites in depressed suicide victims. Brain Res 443: 272–280

Cheetham SC, Cromptom MR, Czudek C, Horton RW, Katona CLE, Reynolds GP (1989) Serotonin concentrations and turnover in brains of depressed suicides. Brain Res 502: 332–340

Cochran E, Robins E, Grote S (1976) Regional serotonin levels in brain: a comparison of depressive suicides and alcoholic suicides with controls. Biol Psychiatry 11: 283–294

Crow TJ, Cross AJ, Cooper SJ, Deakin JFW, Ferrier IN, Johnson JA, Joseph MH, Owen F, Poulter M, Lofthouse R, Corsellis JAN, Chambers DR, Blessed G, Perry EK, Perry RH, Tomlinson BE (1984) Neurotransmitter receptors and monoamine metabolites in the brains of patients with Alzheimer-type dementia and depression, and suicides. Neuropharmacology 23 (12 B): 1561–1569

De Montigny C, Blier P, Chaput Y (1984) Electrophysiologically-identified serotonin receptors in the rat CNS. Neuropharmacology 23: 1511–1520

Fernstrom JD, Wurtman RJ (1971) Brain serotonin content: physiological dependence on plasma tryptophan levels. Science 173: 149–152

Goldberg HL, Finnerty RJ (1979) The comparative efficacy of buspirone and diazepam in the treatment of anxiety. Am J Psychiatry 136: 1184–1187

Goodwin GM, DeSouza RJ, Wood AJ, Green AR (1986) Lithium decreases 5-HT_{1A} and

5-HT_2 receptor and alpha$_2$-adrenoreceptor mediated function in mice. Psychopharmacology 90: 482–487

Hall MD, El Mestikawy S, Emerit MB, Pichat L, Hamon M, Gozlan H (1985) [^{3}H]8-hydroxy-2(di-n-propylamino)tetralin binding to pre- and postsynaptic 5-hydroxytryptamine sites in various regions of rat brain. J Neurochem 44: 1685–1696

Heron DS, Shinitzky M, Hershkowitz M, Samuel D (1980) Lipid fluidity markedly modulates the binding of serotonin to mouse brain membranes. Proc Natl Acad Sci 77: 7463–7467

Hoyer D, Pazos A, Probst A, Palacios JM (1986) Serotonin receptors in the human brain. I. Characterization and autoradiographic localization of 5-HT_{1A} recognition sites. Apparent absence of 5-HT_{1b} recognition sites. Brain Res 376: 85–96

Kirk RE (1982) Experimental design: procedures for the behavioral sciences. Brooks/Cole Publishing Company, Ca, U.S.A.

Kennet GA, Dourish CT, Curzon G (1987) Antidepressant-like action of 5-HT_{1A} agonists and conventional antidepressants in an animal model of depression. Eur J Pharmacol 134: 265–275

Leckman JF, Charney DS, Nelson JC, Heninger GR, Bowers MB (1980) CSF tryptophan, 5-HIAA and HVA in 132 psychiatric patients characterized by diagnosis and clinical state. Recent Adv Neuropsychopharmacol 31: 289–297

Lloyd KG, Farley IJ, Deck JHN, Hornykiewicz O (1974) Serotonin and 5-hydroxyindoleacetic acid in discrete areas of the brainstem of suicide victims and controls patients. Adv Biochem Psychopharmacol 2: 387–397

Mann JJ, Stanley M, McBride PA, McEwen BS (1986) Increased serotonin-2 and β-adrenergic receptor binding in the frontal cortices of suicide victims. Arch Gen Psychiatry 43: 954–959

Marcusson J, Oreland L, Winblad B (1984) Effect of age on human brain serotonin (S-1) binding sites. J Neurochem 43: 1699–1705

McKeith IG, Marshall EF, Ferrier IN, Armstrong NM, Kennedy WN, Perry RH, Perry EK, Eccleston D (1987) 5-HT receptor binding in post-mortem brain from patients with affective disorder. J Affect Dis 13: 67–74

McMillen BA, Scott SM, Williams HL, Sanghera MK (1987) Effects of gepirone, an arylpiperazine anxiolytic drug, on aggressive behavior and brain monoaminergic neurotransmission. Naunyn-Schmiedebergs Arch Pharmacol 335: 454–464

Middlemiss DN, Palmer AM, Edel N, Bowen DM (1986) Binding of the novel serotonin agonist 8-hydroxy-2-(Di-n-propylamino)tetralin in normal and Alzheimer brain. J Neurochem 46: 993–996

Norton WT (1981) Chapter 4. Formation, structure and biochemistry of myelin. In: Siegel GS, Albers RW, Agranoff BW, Katzman R (eds) Basic neurochemistry, pp 63–92

Owen F, Cross AJ, Crow TJ, Deakin JFW, Ferrier IN, Lofthouse R, Poulter M (1983) Brain 5-HT_2 receptor and suicide. Lancet ii: 1256

Owen F, Chambers DR, Cooper SJ, Crow TJ, Johnson JA, Lofthouse R, Poulter M (1986) Serotonergic mechanisms in brains of suicide victims. Brain Res 326: 185–188

Palfreyman MG, Mir AK, Kubina M, Middlemiss DN, Richards M, Tricklebank MD, Fozard J (1987) Monoamine receptor sensitivity changes following chronic administration of MDL 72394, a site-directed inhibitor of monoamine oxidase. Eur J Pharmacol 130: 73–89

Pare CMB, Yeung DPH, Price K, Stacey RS (1969) 5-Hydroxytryptamine, noradrenaline and dopamine in brainstem, hypothalamus, and caudate nucleus of control and of patients committing suicide by coal-gas poisoning. Lancet ii: 133–135

Pedigo NW, Yamamura HI, Nelson DL (1981) Discrimination of multiple [^{3}H]-5-hydroxytryptamine binding sites by neuroleptics spiperone in rat brain. J Neurochem 36: 220–226

Peroutka SJ (1986) Pharmacological differentiation and characterization of 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1C} binding sites in rat frontal cortex. J Neurochem 47: 529–540
Peroutka SJ (1988) 5-Hydroxytryptamine receptor subtypes. Ann Rev Neurosci 11: 45–60
Schoemaker H, Langer SZ (1986) [^{3}H]8-OH-DPAT labels the serotonin transporter in the rat striatum. Eur J Pharmacol 124: 371–373
Schweizer EE, Amsterdam J, Rickels K, Kaplan M, Droba M (1986) Open trial of buspirone in the treatment of major depressive disorder. Psychopharmacol Bull 22: 183–191
Shaw DM, Camps FE, Eccleston EG (1967) 5-Hydroxytryptamine in the hind-brain of depressive suicides. Br J Psychiatry 113: 1407–1411
Shih JC, Ohsawa R (1983) Differential effect of cholesterol on two types of 5-hydroxytryptamine binding sites. Neurochem Res 8: 701–710
Sprouse JS, Aghajanian GK (1986) (-)-Propranolol blocks the inhibition of serotonergic dorsal raphé cell firing by 5-HT_{1A} selective agonists. Eur J Pharmacol 128: 295–298
Stanley M, Mann JJ (1983) Increased serotonin-2 binding sites in frontal cortex of suicide victims. Lancet i: 214–216
Stanley M, McIntrye I, Gershon S (1983) Postmortem serotonin metabolism in suicide victims. Abstract Annual Meeting, American College of Neuropsychopharmacology
Todd RD, Ciaranello RD (1987) Multiple high-affinity [^{3}H]serotonin binding sites in human cortex. Brain Res 400: 247–258
van Praag HM (1983) CSF 5-HIAA and suicide in nondepressed schizophrenics. Lancet ii: 977–978
Verge D, Daval G, Patey A, Gozland H, Mestikawy SER, Hamon M (1985) Presynaptic 5-HT autoreceptors on serotonergic cell bodies and/or dendrites but not terminals are of the 5-HT_{1A} subtype. Eur J Pharmacol 113: 463–464
Verge D, Daval G, Marcinkiewicz M, Patey A, Mistikawy SER, Gozlan H, Hamon M (1986) Quantititavice autoradiography of multiple 5-HT_1 receptor subtypes in the brain of control or 5-7-dihydroxytryptamine-treated rats. J Neurosci 6: 3474–3482
Woolf WA, Youdim MBH, Kuhn DH (1985) Does brain 5-HIAA indicate serotonin release or monoamine oxidase activity? Eur J Pharmacol 109:381–387

Authors' address: H. Y. Meltzer, M.D., University Hospitals of Cleveland, Hanna Pavillion, Room B-68, 2040 Abington Road, Cleveland, OH 44106-5000, U.S.A.

Received October 9, 1990