Brain 5-Hydroxytryptamine Uptake Sites Labeled with [^{3}H]Paroxetine in Antidepressant Drug-Treated Depressed Suicide Victims and Controls

Kevin M Lawrence[1], *Freddy De Paermentier[1], Sandra Lowther[1], M Rufus Crompton[2], Cornelius LE Katona[3], Roger W Horton[1]

[1]Department of Pharmacology and Clinical Pharmacology, St George's Hospital Medical School, London, United Kingdom

[2]Department of Forensic Medicine, St George's Hospital Medical School, London, United Kingdom

[3]Department of Psychiatry, University College London Medical School, London, United Kingdom

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Saturation binding of [^{3}H]paroxetine was performed in 10 brain regions from a group of suicide victims who had a firm, retrospective diagnosis of depression and who had been prescribed antidepressant drugs, as well as in a group of controls. The number of binding sites did not differ significantly between suicide victims and controls, apart from in putamen, where a lower number of sites was found in the suicide victims. Higher dissociation constant (K_d) values were found in suicide victims dying by antidepressant overdose and also in those dying by other means when compared with controls.

Key Words: 5-hydroxytryptamine (5-HT) uptake sites, [^{3}H]paroxetine binding, postmortem human brain, depression, suicide, antidepressant drugs

INTRODUCTION

There is substantial evidence for an association between depressive illness and an abnormality of serotonin (5-hydroxytryptamine [5-HT]) uptake. Blood platelets have been widely studied as a model of neuronal uptake, and many studies have demonstrated a lower maximum velocity of active 5-HT uptake in platelets from drug-free depressed patients compared with controls (Coppen and others 1978; Tuomisto and others 1979; Meltzer and others 1981).

The radioligand [^{3}H]imipramine has been widely used to study 5-HT uptake sites. Many studies have found lower numbers of [^{3}H]imipramine binding sites in platelets from depressed patients compared with controls, although a substantial number have found no differences (Mellerup and Plenge 1988; Elliott 1991). Recent studies have used the more selective 5-HT uptake site ligand [^{3}H]paroxetine, and the vast majority have found no differences in the number of sites between depressed patients and controls (D'Haenen and others 1988; Lawrence and others 1993, 1994; D'Hondt and others 1994; Iny and others 1994; Nankai and others 1994; Hrdina and others 1995; Nelson and others 1995).

There are fewer studies of the 5-HT uptake site in human brain in relation to depression. Results using [^{3}H]imipramine

*Deceased, August 11, 1996.

Address for correspondence: Dr RW Horton, Department of Pharmacology and Clinical Pharmacology, St George's Hospital Medical School, London SW17 ORE, United Kingdom.
e-mail: horton@sghms.ac.uk

Table 1

Drug treatment and cause of death for each suicide victim (N = 13)

Drug treatment	Duration of treatment (weeks)	Cause of death
		Overdose with antidepressant drugs
Trimipramine, temazepam, diazepam	2	Trimipramine, acetylsalicylic acid
Dothiepin, haloperidol	4	Dothiepin, haloperidol
Amitriptyline, diazepam	20	Amitriptyline, acetylsalicylic acid
Dothiepin	38	Dothiepin
Imipramine, lithium, diazepam	40	Imipramine
Amitriptyline	> 52	Amitriptyline
		Overdose without antidepressant drugs
Mianserin	4	Barbiturate, temazepam
Clomipramine, thioridazine, procyclidine	16	Dextropropoxyphene, paracetamol
Imipramine, flupenthixol	> 52	Acetylsalicylic acid
		Violent methods
Amitriptyline	1	Hanging
Amitriptyline	1	Hanging
Dothiepin, temazepam	3	Jumping from a height
Amitriptyline, trifluoperazine, temazepam	11	Hanging

have been conflicting, possibly because under certain assay conditions, [^{3}H]imipramine binds to non-5-HT uptake sites (Hrdina 1984). Studies using [^{3}H]paroxetine, however, have proved consistent. Three studies of suicide victims (Lawrence and others 1990; Andersson and others 1992; Hrdina and others 1993) and 1 study of depressed subjects dying by natural causes (Ferrier and others 1986) have found no significant differences in [^{3}H]paroxetine binding compared with controls. Two of the studies were restricted to suicide victims with a retrospective diagnosis of depression who had been free of antidepressant drugs (Lawrence and others 1990; Hrdina and others 1993). The subjects studied by Andersson and others (1992) were more diverse in relation to diagnosis and drug treatment.

The effect of chronic antidepressants on 5-HT uptake sites is an issue of possible clinical relevance. In some but not all studies, antidepressants have been shown to increase the number of platelet [^{3}H]imipramine binding sites in both depressed patients and healthy volunteers (Braddock and others 1984; Suranyi-Cadotte and others 1985; Cowen and others 1986; Wagner and others 1987; Arora and Meltzer 1988; Healy and others 1990, 1991). In contrast, several studies of chronic antidepressant administration in animals report a decrease in brain [^{3}H]imipramine binding sites (Raisman and others 1980; Plenge and Mellerup 1982; Brunello and others 1987). In keeping with this latter finding, Lesch and others (1993) observed that long-term administration of antidepressants that inhibit 5-HT reuptake decreases 5-HT transporter messenger ribonucleic acid (mRNA) concentrations in rat brain.

The effect of antidepressants on 5-HT uptake sites in the brains of depressed patients has not been reported. In this study, we have examined 5-HT uptake sites labeled with [^{3}H]paroxetine in brain samples obtained postmortem from a small group of suicide victims with a retrospective diagnosis of depression, all of whom had been prescribed antidepressant treatment, and from control subjects individually matched for age, gender, and postmortem delay.

METHODS

Subject selection

Deaths recorded as suicides at coroners' inquests were subjected to retrospective diagnosis by a psychiatrist (CLEK) using hospital and coroners' records and interviews with each subject's general practitioner. Thirteen subjects for whom there was sufficient evidence to establish a retrospective diagnosis of depression (according to the criteria of Beskow and others [1976]) and for whom prescription of antidepressant drugs (alone or in combination with other psychoactive drugs) was clearly documented were selected for study. The duration of drug treatment and the cause of death for the suicide group are shown in Table 1. Controls were subjects without documented evidence of psychiatric illness who died suddenly from causes not involving the central nervous system; control subjects were matched to suicide victims for

Table 2

Demographic details of subjects studied

Group	Number of subjects	Age (y)	Gender	Postmortem delay (h)	Storage time (mo)
Control	11	45 ± 5 (18–69)	6M, 5F	40 ± 5 (18–63)	34 ± 5 (13–64)
Suicide	13	43 ± 3 (16–68)	7M, 6F	35 ± 4 (5–68)	29 ± 6 (7–54)

Data are expressed as means ± SEM; the range is shown in parentheses.

gender, age, and postmortem delay (the time from death to storage of tissue at –80 °C). For 2 suicide victims, no matched control was available. Controls died by myocardial infarction (n = 9), road traffic accident (n = 1), and accidental drowning (n = 1).

Tissue collection, dissection, and storage

Tissue collection, dissection, and storage were performed as previously described by Cheetham and others (1988). Briefly, brains were obtained within 68 h of death and stored at –80 °C. Eighteen hours prior to dissection, brains were transferred to –20 °C. Coronal sections (3 mm thick) were cut and specific areas dissected on a perspex surface cooled with carbon dioxide granules. Great care was taken to include only grey matter in cortical samples. Dissected areas were finely chopped into approximately 3-mm cubes, thoroughly mixed, and stored in air-tight containers at –80 °C until assayed. Brain areas studied were frontal cortex (Brodmann area 10), occipital cortex (Brodmann areas 17/18), temporal cortex (Brodmann areas 21/22 and 38), hippocampus, caudate, thalamus, putamen, amygdala, and substantia nigra.

Tissue preparation

Frozen brain samples were homogenized in ice-cold, 0.25 M sucrose (1:30 weight:volume [w:v]) using a motor-driven, Teflon pestle (8 strokes at 120 revolutions per minute). The homogenate was centrifuged at 1000 × *g* for 10 min to remove cell debris and myelin. The supernatant was stored on ice, and the pellet was rehomogenized in 0.25 M sucrose (1:20 w:v) and centrifuged at 750 × *g* for 10 min. The supernatants were combined and diluted (1:100 w:v) with 50 mM Tris-HCl buffer (pH 7.5) containing 120 mM NaCl and 5 mM KCl and centrifuged at 35 000 × *g* for 10 min. The pellet was resuspended in buffer (1:100 w:v) and recentrifuged at 35 000 × *g* for 10 min. The final pellet was resuspended in an appropriate volume of buffer to give 2.5 mg original wet weight of tissue per tube for substantia nigra, 10 mg for cortical regions, and 5 mg for other regions. All centrifugations were performed at 4 °C.

Binding assay

Assays were carried out in glass tubes in a total volume of 2 mL. Freshly prepared membranes were incubated for 90 min at 22 °C with [^{3}H]paroxetine (specific radioactivity 29 Ci/mmol, NEN Dupont, Boston, USA) at 8 concentrations (9 to 500 pM) in 50 mM Tris-HCl buffer (pH 7.5) containing 120 mM NaCl and 5 mM KCl. Specific binding was defined by 1 μM citalopram. Membrane-bound radioactivity was recovered by filtration under vacuum through Whatman GF/C glass fiber filters using a Brandel cell harvester. Filters were rapidly washed with 16 mL ice-cold buffer and radioactivity determined by liquid scintillation spectroscopy using the Packard scintillator 299 at an efficiency of 39% to 45%. Aliquots of membranes were stored at –20 °C for subsequent protein determination by the method of Lowry and others (1951) using bovine serum albumin as standard. Assays were performed on coded samples blind to subject classification but arranged such that batches contained samples from both subgroups.

Analysis

The maximum number of binding sites (B_{max}) and K_d values were determined by computerized nonlinear regression analysis. Means were compared using the Wilcoxon rank sum test, but for ease of presentation, results are expressed as means ± SEM. Correlations were determined using Kendall's rank correlation.

RESULTS

Demographic details of the subjects studied are shown in Table 2. Age, postmortem delay, and storage time (storage of tissue at –80 °C prior to assay) did not differ significantly between suicide and control subjects. There were no significant correlations between age or postmortem delay and the affinity and number of [^{3}H]paroxetine binding sites in any region.

There were no significant differences in the number of [^{3}H]paroxetine binding sites between suicide victims and controls, except in the putamen, where the number of sites was significantly lower in the suicide group (by 22%) than in the control group (Table 3).

Table 3

[^{3}H]Paroxetine binding in antidepressant-treated suicide victims and controls

	B_{max} (fmol/mg protein)		K_d (pM)	
Brain region	Control group	Suicide group	Control group	Suicide group
Frontal cortex	42 ± 3	45 ± 4	33 ± 5	56 ± 14
Occipital cortex	73 ± 7	78 ± 7	39 ± 6	103 ± 34[a]
Temporal cortex Ba 21/22	41 ± 7	37 ± 3	29 ± 5	49 ± 6[a]
Temporal cortex Ba 38	96 ± 8	105 ± 7	40 ± 5	98 ± 27[b]
Hippocampus	128 ± 15	93 ± 9	34 ± 3	88 ± 20[b]
Caudate	199 ± 18	206 ± 15	34 ± 4	63 ± 14
Thalamus	266 ± 24	272 ± 33	27 ± 1	66 ± 16
Putamen	214 ± 32	167 ± 13[a]	32 ± 2	94 ± 20[b]
Amygdala	279 ± 21	278 ± 25	32 ± 2	48 ± 7
Substantia nigra	557 ± 35	514 ± 48	23 ± 2	47 ± 13

Values are mean ± SEM; Ba = Brodmann area.
[a]$P < 0.05$ (Wilcoxon rank sum test).
[b]$P < 0.01$ (Wilcoxon rank sum test).

K_d values were higher in suicide victims compared with controls in all the brain regions studied (see Table 3), and differences reached statistical significance in occipital cortex (Brodmann areas 17/18), temporal cortex (Brodmann areas 21/22 and 38), hippocampus, and putamen.

DISCUSSION

We have previously examined [^{3}H]paroxetine binding in brain samples from suicide victims with retrospective diagnoses of depression who had not received antidepressants in the previous 3 mo (Lawrence and others 1990). We found no differences in the number or affinity of sites in 10 brain areas compared with matched controls. Two subsequent studies in suicide victims also found no differences in the number of [^{3}H]paroxetine binding sites compared with controls (Andersson and others 1992; Hrdina and others 1993). Thus there is no evidence to date that suicide per se or suicide in depressed subjects is associated with altered numbers of brain [^{3}H]paroxetine binding sites.

In the present study, we measured [^{3}H]paroxetine binding in brain samples from a group of subjects who had been prescribed antidepressant drugs, committed suicide, and were given retrospective diagnoses of depression. Except in putamen (discussed below), the number of [^{3}H]paroxetine binding sites did not differ from matched controls. Thus the present results give no indication that antidepressant administration in depressed subjects is associated with adaptive changes in 5-HT uptake sites. This conclusion must be regarded as preliminary, however, for several reasons. The number of subjects studied was small. Treatment was diverse; although most subjects had been prescribed tricyclic antidepressants, some had also received other psychoactive drugs, such as benzodiazepines or antipsychotics (see Table 1). There are inevitably uncertainties regarding compliance, but therapeutic concentrations of antidepressants were present in blood samples taken at postmortem examination in all subjects in the suicide group (after excluding those who had taken antidepressant overdoses). Six of the subjects studied had been prescribed antidepressants for 4 weeks or less. This may be insufficient time for adaptive changes to develop fully. The remaining 7 subjects had been prescribed antidepressants for a minimum of 11 weeks, however, and [^{3}H]paroxetine binding in these subjects did not differ significantly either from their matched controls or from subjects who had been prescribed antidepressants for shorter intervals.

Two other lines of evidence also provide support for the view that antidepressants do not change the number of 5-HT uptake sites labeled with [^{3}H]paroxetine. We have previously reported that treatment of depressed patients with fluoxetine or lofepramine for 6 weeks did not alter the number of platelet [^{3}H]paroxetine binding sites from pretreatment values (Lawrence and others 1994). In addition, several studies have demonstrated that the number of [^{3}H]paroxetine binding sites is unaltered in rat cortex following chronic administration of a range of antidepressants or following repeated electroconvulsive shock (Graham and others 1987; Gleiter and Nutt 1988; Cheetham and others 1993).

In the present study, we found a significantly lower number of [^{3}H]paroxetine binding sites in the putamen of suicide victims compared with controls. It could be argued that a difference in 1 brain area out of the 10 studied might arise by chance. We have other evidence, however, to indicate this is unlikely to be the case. We have previously reported lower concentrations of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) and lower numbers of [^{3}H]paroxetine binding sites restricted to the putamen in antidepressant-free depressed subjects who committed suicide (Cheetham and others 1989; Lawrence and others 1990). It therefore seems unlikely that the present finding occurred merely by chance or that it was related to antidepressant treatment. The lower concentrations of 5-HT and 5-HIAA, taken together with the lower number of [^{3}H]paroxetine binding sites, are compatible with a loss of presynaptic 5-HT nerve terminals. Some studies have provided evidence for an involvement of the basal ganglia in affective disorders. Buchsbaum and others (1986) demonstrated that the metabolic rate for glucose in the basal ganglia of patients with affective disorders was significantly lower than the rate for controls. Of particular relevance is the study of Husain and others (1991), which determined that the volume of putamen nuclei (assessed by in vivo magnetic resonance imaging) in patients with major depression was markedly lower than in controls. This finding provides a possible anatomical correlate for our neurochemical evidence of abnormal presynaptic 5-HT markers in the putamen of depressed suicide victims. If these biochemical changes are related to depression, it would be reasonable to expect them to be independent of the method of suicide. This does not appear to be the case. In our previous studies, the reduction of presynaptic 5-HT markers in the putamen was restricted to subjects who committed suicide by nonviolent methods (drug overdose or carbon monoxide poisoning); we followed the same procedure in the present study, in which 9 of the 13 suicide subjects died by nonviolent means. It seems reasonable, therefore, to conclude that presynaptic 5-HT nerve terminals in the putamen are particularly vulnerable to some aspect of nonviolent death. This could possibly be antemortem hypoxia (since this is likely to be a common feature of death due to drug overdose or carbon monoxide poisoning), although we have no firm evidence to support that hypothesis.

Another feature of the present study was a marked increase in K_d values for [^{3}H]paroxetine binding in the victims of suicide compared with controls, an increase presumably attributable to the continued presence of antidepressant drugs in the membrane preparations, despite the washing procedure. Not surprisingly, the most marked increases (up to 6 times control values) were observed in those subjects who died following antidepressant overdosage. There were also increases in K_d values, however, in subjects who died by physical means or as a result of overdosage with drugs other than antidepressants. While this provides further evidence that the subjects were actually taking their prescribed drugs, it also illustrates the difficulty in completely removing drugs from membrane homogenates by extensive washing. The present findings in subjects who had died by methods other than antidepressant overdosage are consistent with our previous report of an approximate doubling of K_d values for [^{3}H]paroxetine binding in platelet membranes from antidepressant-treated depressed patients (Lawrence and others 1994).

In conclusion, this study of a small group of suicide victims with diverse treatment provides no evidence that antidepressant treatment alters the number of [^{3}H]paroxetine binding sites in human brain.

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