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Differential Involvement of 5-HT$_{1B/1D}$ and 5-HT$_6$ Receptors in Cognitive and Non-cognitive Symptoms in Alzheimer's Disease

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Growing evidence suggests that a compromised serotonergic system plays an important role in the pathophysiology of Alzheimer's disease (AD). We assessed the expression of 5-HT$_{1B/1D}$ and 5-HT$_6$ receptors and cholinacetyltransferase (ChAT) activity in *post-mortem* frontal and temporal cortex from AD patients who had been prospectively assessed for cognitive function using the Mini-Mental State Examination (MMSE) and behavioral changes using the Present Behavioral Examination (PBE). 5-HT$_{1B/1D}$ and 5-HT$_6$ receptor densities were significantly reduced in both cortical areas. 5-HT$_{1B/1D}$ receptor density was correlated to MMSE decline in the frontal cortex, supporting its implication in memory impairment. The best predictor for lowered 5-HT$_6$ receptor density in the temporal cortex was the PBE measure of overactivity. The 5-HT$_6$/ChAT ratio was related to aggression both in the frontal and temporal cortex. Therefore, antagonists acting at 5-HT$_6$ receptors could be useful in the treatment of non-cognitive symptoms associated to AD.
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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder defined by the decline of memory and cognitive function. Neurochemically, the classical hallmark of AD is the disruption of basal forebrain cholinergic pathways and consequent cortical cholinergic denervation of the neocortex and hippocampus. This cholinergic dysfunction has been largely related to cognitive disturbances (Perry *et al*, 1992; Perry *et al*, 1999; Sarter and Bruno, 1997). In addition to these cognitive symptoms, most patients will suffer from neuropsychiatric symptoms called 'behavioral and psychological symptoms of dementia' (BPSD) (IPA, 1996). BPSD such as depression, overactivity, psychosis, or aggressive behavior occur frequently in AD patients and are the major factor that leads to early institutionalization of the patient (Levy *et al*, 1999; Martinson *et al*, 1995; Parnetti *et al*, 2001). BPSD are not merely an epiphenomenon of cognitive impairment, but could be attributed to specific biological brain dysfuction. However, the neurochemical correlates of these dysfunctions are not yet fully understood (Esiri, 1996). A number of studies have shown beneficial effects in the treatment of BPSD with acetylcholinesterase inhibitors (reviewed by Parnetti *et al*, 2001). However, given the diversity of BPSD, it is likely that other neurotransmitter systems contribute to such behaviors.

Extensive evidence on serotonergic denervation in AD has been reported (Chen *et al*, 2000; Gottfries, 1990; Palmer *et al*, 1987a), although its clinical significance has only been partially defined. 5-HT may play a role in higher cognitive processes such as memory and learning (Buhot, 1997; Buhot *et al*, 2000) and it has been suggested that many of the serotonin actions could be mediated by a modulation of the cholinergic system (Buhot, 1997; Buhot *et al*, 2000). In addition, even though there is no specific center in the brain for a distinctive BPSD, the organization of the ascending serotonergic neuron projections and the widespread distribution of serotonergic terminals in cortical and limbic areas indicate that these projections are the most likely to be involved in the regulation of behavioral and mood disorders (Barnes and Sharp, 1999). In this sense, the serotonergic system has been widely implicated in depression (Chen *et al*, 1996; Meltzer *et al*, 1998), psychosis (Garcia-Alloza *et al*, submitted; Jones and Blackburn, 2002), and aggression (Berman, 1997; Procter *et al*, 1992).

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The involvement of several different serotonergic receptors in the symptoms of AD has been previously explored (Cheng *et al*, 1991; Cross, 1990; Lai *et al*, 2002; Palmer *et al*, 1987b). However, to date, there are no studies on 5-HT$_{1B/1D}$ or 5-HT$_6$ receptors, which may be of special interest in AD. Specifically, the 5-HT$_{1B/1D}$ receptor has been shown to modulate cholinergic activity in animals (Cassel *et al*, 1995; Maura and Raiteri, 1986; Sarham and Fillion, 1999) and it has also been implicated in consolidation of learning (Meneses and Hong, 1997; Meneses *et al*, 1997; Meneses, 2001). The function(s) of the 5-HT$_6$ receptor, although not completely understood, include the potential regulation of putative cholinergic-mediated behaviors (Bentley *et al*, 1999; Bourson *et al*, 1995), anxiety (Otano *et al*, 1999), and memory performance (Rogers and Hagan, 2001; Woolley *et al*, 2001a, b). 5-HT$_6$ receptor antagonists have also been shown to enhance basal glutamatergic (Dawson *et al*, 2000; Dawson *et al*, 2001), cholinergic (Shirazi-Southall *et al*, 2002; Riemer *et al*, 2003), and potentiated dopaminergic (Dawson *et al*, 2003) neurotransmission. The localization of this 5-HT$_6$ receptor in limbic and cortical regions, and the high affinity of atypical antipsychotic drugs such as clozapine for the receptor, also suggest the possible involvement of the receptor in the pathogenesis of schizophrenia (reviewed by Branchek and Blackburn, 2000).

In this study, we tested the hypothesis that disturbances of the serotonergic 5-HT$_{1B/1D}$ and 5-HT$_6$ receptors may contribute to the cognitive impairment and/or BPSD in AD. We have studied 5-HT$_{1B/1D}$ and 5-HT$_6$ receptors binding in two cortical areas (Brodmann area 10 (BA10) and Brodmann 20 (BA20)) of AD patients with respect to cognitive impairment and four behavioral syndromes (psychosis, overactivity, aggressive behavior, and depression) prospectively assessed in this patient group (Hope *et al*, 1997). Cholinergic hypofunction was evaluated by comparing ChAT levels between control and AD patients.

MATERIALS AND METHODS

Patients and Assessment of Behavior

For all subjects, consent for *post-mortem* examination and for the use of tissue for research was obtained from a close relative. The study had full local ethics committee approval (Radcliffe Infirmary, Oxford). A total of 42 individuals were included in the study, 21 patients with a clinical diagnosis of dementia and 20 elderly normal control cases. Those patients with dementia were an autopsied subset of subjects included in a prospective study of behavioral changes in clinically diagnosed demented patients (Hope *et al*, 1997). Initially, all patients were living in community with a caregiver (usually spouse or daughter) who could accurately report day-to-day behavior. More than one assessor was assigned to institutionalized patients when necessary. Drug histories were recorded for all patients; 13 patients were taking major tranquilizers and eight were taking minor tranquilizers. None of the patients with AD received cholinomimetics. At entry to the study, assessment and diagnoses were made using CAMDEX (Roth *et al*, 1986), DMS-III-R criteria (American Psychiatric Association, 1987), and NINCDS-ADRA criteria (McKhann *et al*, 1984). Cognitive status was assessed at four monthly intervals using the Mini-Mental State Examination (MMSE) (Folstein *et al*, 1975). Decline in MMSE was calculated as the difference between maximum scoring and the scoring obtained the last time the patient was examined before death.

Four behavioral and psychological syndromes were assessed using the Present Behavioral Examination (PBE) (Hope and Fairburn, 1992): depression, overactivity, psychosis, and aggressive behavior (Hope *et al*, 1997). Briefly, the PBE is a standardized, caregiver-based interview with high intra- and inter-rater reliability that covers in detail the observable behavior and mental state of the patient. Questions to elucidate the caregiver answers were also included. The depression factor was the sum of four components: apparent sadness, gloomy thoughts, feeling like a failure, and tearfulness. The overactivity factor consisted of the total of the highest ratings for walking and trailing + checking. The psychosis factor was the sum of scores for hallucinations, persecutory ideas, and inappropriate anxiety. Three different aspects of aggressive behavior were used in this analysis. These were physical aggression, aggressive resistance, and verbal aggression (Keene *et al*, 1999), and the highest ratings were added together to give the aggressive behavior factor. Each component of the syndrome was scored from 0 to 2. A score of 0 meant that the behavior was absent. A score of 1 (mild) denoted that that particular type of behavior had occurred on up to half the days in the previous weeks. A rating of 2 (severe) meant that the behavior had occurred on half of the days or more. This gives a maximum score of 6 (or 8 for the depression factor). Factors were calculated from behavioral data for the last interview before death in order to correlate them with neurochemical data determined *post-mortem*.

Tissue Samples and Neuropathology

At autopsy, brains were removed and blocks corresponding to the frontal (BA10) and temporal (BA20) cortex were removed and stored at -80°C until processed. All suspected AD cases were found to meet CERAD criteria for a diagnosis of AD (Mirra *et al*, 1991). Blocks of tissue were carefully chosen. Pieces were taken from each block and were divided in parts in order to perform the consequent experiments. To partially mitigate the possible effects of the cause of death on neurochemical determinations, brain pH was measured as an index of acidosis associated with terminal coma (Table 1). Brain pH is used as an indication of tissue quality in *post-mortem* research, with pH $>$ 6.1 considered to be acceptable (Bahn *et al*, 2001). It is also important to note that it is accepted that ligand binding to receptors does not appear to differ substantially as a function of brain pH (Lewis, 2002).

Cholinergic hypofunction in both cortical regions was assessed by means of ChAT activity. This assay was performed according to the method described by Fonnun (1975).

All subsequent analyses were performed blind to clinical information.

[^{3}H]-GR-125743 Binding

Binding of [^{3}H]-GR-125743 (80 Ci/mmol, NEN, UK) to the 5-HT$_{1B/1D}$ receptor was performed essentially as described

Table 1 Demographic details and cognition status of control and patients with AD for neurochemical determinations.

	Control (n = 20)	Alzheimer (n = 21)
Mean age (years)	74.75 ± 2.67	80.56 ± 1.70
Gender (male/female)	11/9	10/13
Post-mortem delay (hours)	39.28 ± 5.40	48.63 ± 6.30
pH	6.28 ± 0.16	6.44 ± 0.10
MMSE at death	N.D.	5 ± 1
Mean MMSE decline	N.D.	10 ± 2

Values are mean ± S.E.M. MMSE (Mini-Mental State Examination); pH, standard chemical symbol, negative log of hydrogen ion concentration; S.E.M. (Standard error of the mean).

by Domenech *et al* (1997). In brief, partially thawed brain samples were suspended in 20 vol of 50 mM Tris-HCl buffer (pH 7.7) at 4°C and homogenized with an Ultra-turrax T25 (IKA, Germany) homogenizer. The membranes were pelleted by centrifugation (40 000 *g* at 4°C for 15 min) and washed with the same buffer and recentrifuged (4000 *g* at 4°C for 15 min). The final membrane pellet was resuspended in binding buffer (50 mM Tris-HCl, pH 7.7, containing 4 mM $CaCl_2$, 0.1% ascorbic acid, and 10 μM pargyline). Membranes were frozen in aliquots at −20°C until used.

Binding assays were performed in duplicate in 400 μl total volume containing 200 μl of tissue homogenates, 100 μl of [^{3}H]-GR-124543 (0.4–4 nM), and 100 μl of buffer or 5-HT (Sigma, UK) 1 μM to define total and nonspecific binding, respectively. Tubes were incubated at 37°C for 30 min.

[^{125}I]-SB-258585 Binding

Binding of [^{125}I]-SB-258585 (2000 Ci/mmol) to the 5-HT$_6$ receptor was performed as described by Hirst *et al* (2000) with minor modifications. Tissue samples from BA10 and BA20 were partially thawed and homogenized in 10 vol of ice-cold 50 mM Tris-HCl buffer (pH 7.7) using an Ultra-turrax T25 (IKA, Germany) homogenizer. The homogenates were centrifuged at 35 000 *g* for 20 min and the resulting pellet was rehomogenized and incubated at 37°C for 15 min. Following two further centrifugations, membranes were finally resuspended (approximately 80 mg tissue/ml) and stored at −80°C until use.

Binding assays consisted of 320 μl of membrane suspension (corresponding approximately to 8 mg tissue), 40 μl of unlabeled SB-258585 at concentrations from 1 to 10 nM, and 40 μl of 1 nM [^{125}I]-SB-258585, to give a final concentration of 0.1 nM. Nonspecific binding was determined in the presence of 10 μM SB-214111.

5-HT$_{1B/1D}$ and 5-HT$_6$ Binding Measurements

At conclusion of the 5-HT$_{1B/1D}$ and 5-HT$_6$ receptor binding incubation, tubes were rapidly filtered under reduced pressure using a cell harvester (Brandel, USA) using GF/B filters (Whatman, UK) that had been presoaked in 0.3% v/v polyethylenimine (Sigma, UK) in ice-cold wash buffer (50 mM Tris-HCl, pH 7.7). The amount of radioactivity bound to filters was measured in a liquid scintillation counter (Rackbeta 1214, LKB-Wallac). All determinations were carried out in duplicate. Data were subject to Scatchard analysis to determine the number of binding sites (B_{max}: fmol/mg of protein) and the dissociation constant (K_d: nM). Protein content was measured using the assay described by Bradford (1976), using bovine serum albumin (Fraction V, Sigma-Aldrich, Germany) as standard.

Statistical Analysis

Data were analyzed by SPSS for Windows, release 11.0. Student's *t*-test was used in initial comparisons between control patients and patients with AD. The effects of demographic factors (age, *post-mortem* delay, and brain pH) on neurochemical variables were determined by Pearson's product moment. Intercorrelation of neurochemical variables was examined by Pearson's product moment. Spearman's rank correlation was also used for studies of the relationships between severity of dementia (MMSE nearest to death) and neurochemical measures. Multiple regression analysis using the 'stepwise' method was used to investigate possible relationships between neurochemical variables and behavioral syndromes. This allows for the fact that individual patients may show more than one behavioral syndrome and indicates the strongest correlate.

RESULTS

Demographic details of subjects are shown in Table 1. There were no significant correlations between age, *post-mortem* delay, or brain pH and any of the neurochemical variables studied in either control patients or those with dementia ($p > 0.05$) and therefore none of these factors was included as a covariate in subsequent analysis. No influence of pharmacological treatment on the biochemical markers studied was found.

Last scores for BPSD assessed by PBE in AD patients were as follows: depression factor 3 ± 0; overactivity 3 ± 0; psychosis 2 ± 0; aggressive behavior 5 ± 0.

ChAT activity both in the frontal and temporal cortex from AD patients was significantly lower than control patients. Reductions observed reached 28.06 ± 3.71% in BA10 and 40.41 ± 4.29% in BA20.

[^{3}H]-GR-125743 Binding

The 5-HT$_{1B/1D}$ receptor density both in BA10 and BA20 from AD brains was significantly reduced from that measured in control cortical areas. 5-HT$_{1B/1D}$ density reductions in AD brains reached 25% in the frontal cortex and 37% in the temporal cortex (Figure 1).

5-HT$_{1B/1D}$ receptor binding affinity, expressed as K_d, in AD brains was not significantly different from that observed in control brains in both BA10 (control = 0.27 ± 0.03 nM; AD = 0.32 ± 0.03 nM, $p > 0.05$) and BA20 (control = 0.42 ± 0.03 nM; AD = 0.42 ± 0.04 nM, $p > 0.05$).

[^{125}I]-SB-258585 Binding

The density of the 5-HT$_6$ receptor in the frontal and temporal cortex from AD patients was significantly lower

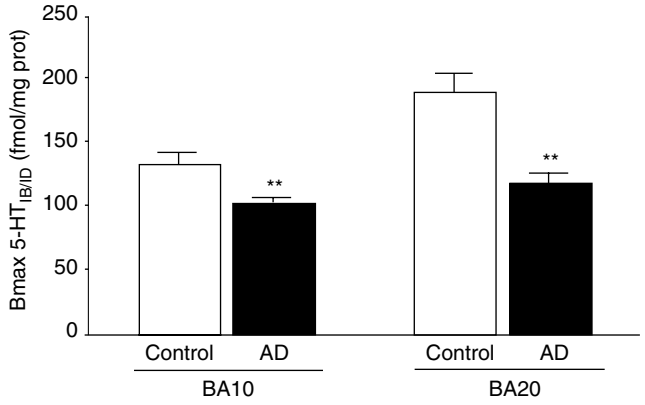

Figure 1 Reductions in 5-HT$_{1B/1D}$ receptor density (expressed as B_{max}: fmol/mg protein) in BA10 and BA20 from control ($n=20$) and AD patients ($n=21$). **Significantly lower than control, Student's *t*-test, *p*<0.01.

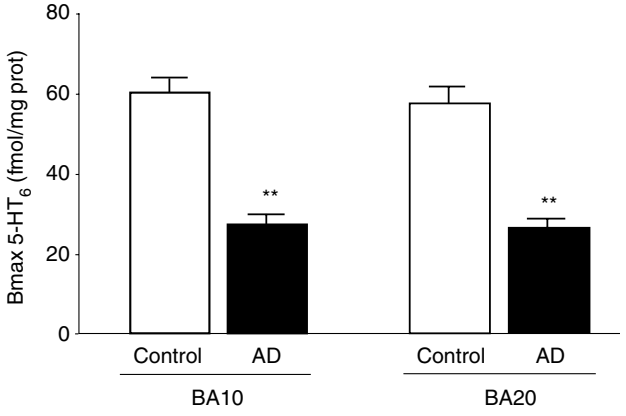

Figure 2 Reductions in 5-HT$_6$ receptor density (expressed as B_{max}: fmol/mg protein) in BA10 and BA20 from control ($n=20$) and AD patients ($n=21$). **Significantly lower than control, Student's *t*-test, *p*<0.01.

than control patients. The reductions observed reached 56% in BA10 and 58% in BA20 (Figure 2).

Receptor binding affinity to 5-HT$_6$ receptors was not affected in AD brains. Control K_d values in BA10 (1.08 ± 0.14 nM) or BA20 (0.68 ± 0.10 nM) were not significantly different from that observed in AD brain membranes (BA10 $= 0.86 \pm 0.14$ nM; BA20 $= 0.84 \pm 0.12$ nM).

Relationship Between 5-HT$_{1B/1D}$ and 5-HT$_6$ Receptors

As shown in Figure 3, 5-HT1B/1D and 5-HT6 receptor densities were significantly correlated both in the frontal and temporal cortex from AD brains.

Relationship Between Neurochemical Variables with the Cognitive Status and Behavioral Syndromes

Spearman's rank correlation showed a statistically significant positive correlation between 5-HT$_{1B/1D}$ receptor density in BA10 and MMSE decline in AD patients (Figure 4). The ratio of 5-HT$_{1B/1D}$ to ChAT levels in BA10 was also negatively correlated with the last MMSE before death ($n=19$; $r=-0.584$**; $p<0.01$). Stepwise multiple regressions revealed no correlation between the density of

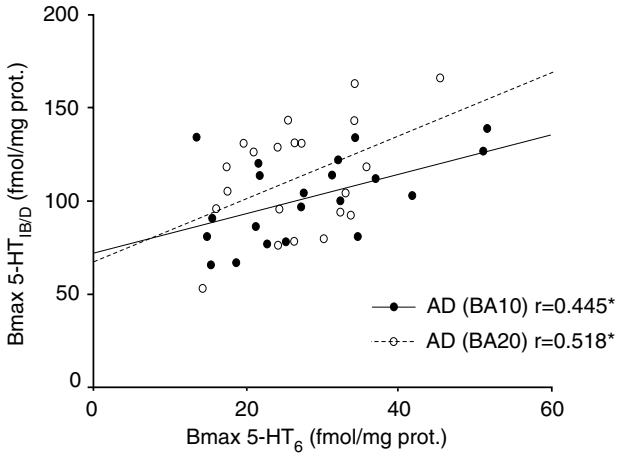

Figure 3 Correlations between 5-HT$_{1B/1D}$ and 5-HT$_6$ receptor densities (B_{max}: fmol/mg protein) in BA10 and BA20 from AD patients ($n=21$). Control (BA10) $r=0.300$; (BA20) $r=-0.112$. *Statistically significant, Pearson's product moment, *p*<0.05.

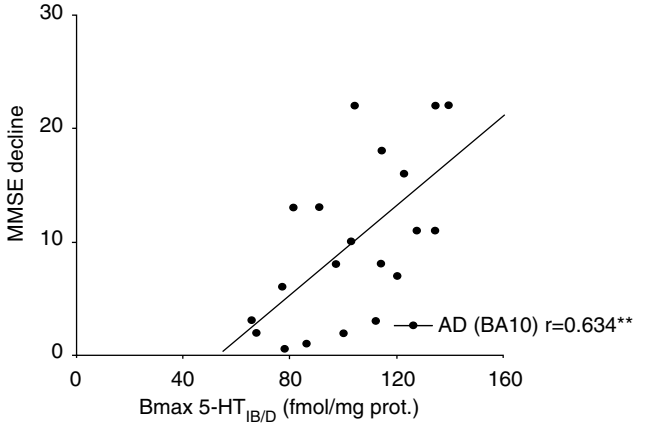

Figure 4 Correlations between 5-HT$_{1B/1D}$ receptor density (B_{max}: fmol/mg protein) in BA10 and MMSE decline in AD patients ($n=20$). *Statistically significant, Pearson's product moment, *p*<0.01.

5-HT$_{1B/1D}$ receptor binding sites, either in BA10 or BA20, and any of the behavioral syndromes determined in patients with dementia.

5-HT$_6$ receptor densities in BA10 or BA20 from AD patients were unrelated to cognitive status before death, using Spearman's rank correlation. Stepwise multiple regression indicated that overactivity was the best predictor for 5-HT$_6$ reduced levels in BA20 ($n=18$; adjusted $r^2=0.401$; $p<0.05$).

It was found that the ratio between 5-HT$_6$ and ChAT in both BA10 ($n=19$, adjusted $r^2=0.206$; $p<0.05$) and BA20 ($n=19$, adjusted $r^2=0.374$; $p<0.01$) was correlated to aggression factor ($n=$, adjusted $r^2=0.226$; $p<0.031$).

DISCUSSION

Reduction of 5-HT as well as its metabolites levels have been reported in *post-mortem* AD brains (Gottfries, 1990; Nazarali and Reynolds, 1992; Sparks *et al*, 1992; Garcia-Alloza *et al*, submitted), and the raphe nucleus is a

preferential site for neurofibrillary tangle formation and neuronal loss in AD (Curcio and Kemper, 1984). Despite the fact that alterations in markers of serotonergic innervation have been linked to clinical indices of cognition and behavioral abnormalities in AD (Chen *et al*, 1995; Chen *et al*, 1996; Forstl *et al*, 1994; Linnoila and Virkkunen, 1992; Zubenko *et al*, 1991), the role of the different serotonergic receptors in the illness remains unclear. Alterations in the expression of serotonergic receptors such as 5-HT$_{1A}$, 5-HT$_2$, or 5-HT$_4$ receptors have already been described in AD (Cheng *et al*, 1991; Cross, 1990; Lai *et al*, 2002; Palmer *et al*, 1987b), whereas the density of 5-HT$_3$ receptors does not seem to be affected by the illness (Barnes *et al*, 1990). To our knowledge, this is the first work describing the involvement of 5-HT$_{1B/1D}$ and 5-HT$_6$ receptors in AD. Important limitations to consider in the study are the *post-mortem* delay and available clinical details. However, similar *post-mortem* delays to those used in the present study have been described in bibliography to measure biochemical markers, ie Lai *et al*, 2001.

A significant decrease in the expression of 5-HT$_{1B/1D}$ receptors in AD *post-mortem* cortical tissue has been found in the present study. Therefore, reductions in 5-HT$_{1B/D}$ expression could reflect the loss of neural populations in AD. On the other hand, these receptors are known to act as inhibitory autoreceptors in axon terminals of serotonergic neurons and as inhibitory heteroreceptors in non-serotonergic neurons (Davidson and Stanford, 1995; Johnson *et al*, 1992). One of their principal functions as heteroreceptors is the inhibition of acetylcholine release (Maura and Raiteri, 1986; Raiteri *et al*, 1989). Following this argument, reductions in 5-HT$_{1B/1D}$ receptors may represent an effort to restore cortical acetylcholine levels in a deteriorated cholinergic system. Consistent with this hypothesis, the present study reports a positive correlation of 5-HT$_{1B/1D}$ receptor density to cognitive decline (greater decline associated with more receptors) in BA10 from AD patients. Agonists acting at 5-HT$_{1B/1D}$ receptors impair learning and memory, and knock-out mice lacking this receptor exhibit a learning facilitation (Cassel *et al*, 1995; Sarham and Fillion, 1999; Wolff *et al*, 2003). It has been suggested that 5-HT$_{1B/D}$ receptor inverse agonists or antagonists have potential utility in the treatment of memory impairments (Meneses and Hong, 1997). Given the role of 5-HT$_{1B/1D}$ receptors in acetylcholine release, it has also been argued that the effects of 5-HT$_{1B/1D}$ agents in cognition could be mediated through the modulation of the cholinergic system. In this sense, the 5-HT$_{1B/D}$/ChAT ratio was also correlated to MMSE decline, suggesting that in situations of cholinergic deficit, the blockade of 5-HT$_{1B/D}$ receptors could have potential enhancing cognitive actions. It is also possible to hypothesize that there is a preservation of these receptors in advanced stages of the disease due to the lack of inhibitory cholinergic activation.

The 5-HT$_6$ receptor is the latest serotonin receptor to be identified by molecular cloning. Its high affinity for antipsychotic drugs, such as clozapine, and its distribution in the brain has stimulated significant interest on its pathophysiological functions (reviewed by Branchek and Blackburn, 2000; Reavill and Rogers, 2001). 5-HT$_6$ is believed to be predominantly postsynaptic, and immunohistochemical data suggest that it may be located on GABAergic spiny neurons in the striatum (Gerard *et al*, 1997; Hamon *et al*, 1999) and in GABAergic/peptidegic striatopalladial and striatal nigro output pathways (Ward and Dorsa, 1996). More recent data have demonstrated colocalization of glutamic acid decarboxylase (GAD) and 5-HT$_6$ receptors in rat cerebral cortex and hippocampus (Fone, 2000). The observation of a significant correlation between HT$_{1B/1D}$ and 5-HT$_6$ receptor densities both in the frontal and temporal cortex from AD patients may indicate that both postsynaptic receptors are located in the same neuronal population that degenerates in the illness. The fact that this correlation was not observed in controls led us to suggest that these mechanisms are related to AD, but not to normal aging.

In contrast to the 5-HT$_{1B/1D}$ data, the reduction in 5-HT$_6$ receptor density was unrelated to cognitive status before death, as measured by MMSE. This is despite good preclinical data describing that 5-HT$_6$ receptor antagonists improve cognitive processes in animals (Riemer *et al*, 2003; Rogers and Hagan, 2001; Woolley *et al*, 2001a; Woolley *et al*, 2001b) and may be attributed to the global nature of the MMSE.

Regarding a role for 5-HT$_6$ receptors in BPSD, their relative abundance in some limbic regions and the high affinity of some antipsychotics to 5-HT$_6$ receptors suggest that they might be involved in the pathogenesis of schizophrenia and other mood disorders (Otano *et al*, 1999; Sleight *et al*, 1997; Tecott *et al*, 1998). The observed correlation between 5-HT$_6$ receptor density in BA20 and overactivity could be consistent with other studies performed in rats treated with antisense 5-HT$_6$ oligonucleotides (Otano *et al*, 1999) or 'knock-out' mice (Tecott *et al*, 1998) which showed increased anxiety. However, it is important to note that while cognitive syndromes deteriorate progressively over the course of AD, many of the behavioral syndromes occur episodically and in subgroups of patients during the disease (Sweet *et al*, 2000). This implies that the neurological basis of the behavioral changes of AD is dynamic and more consistent with a functional biochemical rather than a static structural cause (Levy *et al*, 1999). In this sense, the 5-HT$_6$/ChAT ratio was related to aggressive behavior, both in BA10 and BA20. Accepting the localization of 5-HT$_6$ receptors upon cholinoceptive neurons that disappear in AD (as reflected by the loss of ChAT), the use of 5-HT$_6$ antagonists could be taken as a pharmacological alternative in the treatment of BPSD associated to AD (Miguel-Hidalgo, 2001).

In conclusion, from the present results it is possible to conclude that pharmacological manipulation of the serotonergic system may improve not only cognitive function but also behavioral disturbances in dementia. Thus, in situations of cholinergic deficit, the blockade of 5-HT$_{1B/1D}$ receptors could have enhancing cognitive actions, and 5-HT$_{1B/1D}$ receptor antagonists represent potential new drugs for the treatment of learning and memory dysfunctions in AD. Furthermore, 5-HT$_6$ antagonists represent a potentially new therapeutic approach for the treatment of BPSD associated with AD, a significant improvement on traditional treatments for psychosis in AD where the presently prescribed neuroleptics, which block dopamine D$_2$ receptors and have extrapyramidal side effects in addition to putative anticholinergic side effects, are the only treatment.

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