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Histamine H3 Receptor Characterization in Alzheimer's Disease Brain and Amyloid Over-expressing TASTPM Mice

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Abstract

Context and objective: The potential application of histamine H3 receptor antagonists in the treatment of several central nervous system illnesses, such as Alzheimer's disease (AD), is presently being investigated. Little is now understood regarding the condition of H3 receptors in AD. Method of experimentation: In the current work, we examined H3 receptor binding in post-mortem human AD brain tissues and the amyloid over-expressing double mutant APPswe ¥ PSI.MI46V (TASTPM) transgenic mouse model of AD using the radiolabelled H3 receptor antagonist [3H]GSK189254.

Important outcomes: There were no discernible variations in the particular H3 receptor binding in the brain, hippocampus, or hypothalamus between wild type and TASTPM mice. Sections of human medial frontal cortex from AD brains with varied disease severity (Braak stages) showed specific [3H]GSK189254 binding. 1-VI). We found that, in both frontal and temporal cortical regions, there was no significant difference in H3 receptor densities between AD and age-matched control brains, after conducting a more thorough quantitative investigation on a larger cohort. In contrast, those in the AD group with more advanced dementia prior to death had increased [3H]GSK189254 binding density in the frontal cortex.

Inferences and conclusions: Given the possible use of H3 antagonists as a novel therapeutic approach for the symptomatic treatment of AD, the preservation of H3 receptor integrity shown throughout the various phases of AD in this study is significant.

Keywords: H3 receptor; Alzheimer's Disease; [3H] GSK189254; TASTPM mouse; Neocortex

Introduction

Deficits in several neurotransmitter systems are hallmarks of Alzheimer's disease (AD), and it is thought that these deficiencies lead to both cognitive failure and neuropsychiatric behavior. One of the most noticeable and constant aspects of AD is the loss of cholinergic neurons in the basal forebrain (Whitehouse et al., 1982). This finding served as justification for the creation of cholinergic replacement medications, such as acetylcholinesterase inhibitors (Bartus et al., 1982) [1]. While deficits in 5-hydroxytryptaminergic, GABAergic, noradrenergic, and dopaminergic pathways have also been described, the degree to which these correlate with cognitive and/or behavioral changes in AD can vary (Ramirez et al., 2005). Glutamatergic pyramidal neurons of the cortex and hippocampus also experience prominent cell loss (Greenamyre et al., 1988). The quantity of a specific receptor Alzheimer's disease (AD) is characterized by impairments in many neurotransmitter systems; it is believed that these deficiencies cause cognitive impairment as well as neuropsychiatric behavior [2,3]. The loss of cholinergic neurons in the basal forebrain is one of the most obvious and consistent features of AD (Whitehouse et al., 1982). Acetylcholinesterase inhibitors and other cholinergic replacement drugs were developed in response to this discovery (Bartus et al., 1982) [4]. Although deficiencies in the GABAergic, dopaminergic, noradrenergic, and 5-hydroxytryptaminergic pathways have also been reported, there is variation in the degree to which these correspond with behavioral and/or cognitive abnormalities in AD (Ramirez et al., 2005) [5]. Significant cell loss also occurs in glutamatergic pyramidal neurons of the cortex and hippocampus (Greenamyre et al., 1988).

The amount of a particular receptor The AD brain exhibits modulations in neurotransmitter pathways, such as reduced 5-HT2A receptors in the temporal cortex as compared to age-matched controls (Lai et al., 2005). Although there are contradicting data, it is difficult to determine the significance of the histaminergic system's involvement in AD (Fernández-Novoa & Cacabelos, 2001) [6,7]. For instance, it has been noted that the hippocampus, basal ganglia, and temporal and frontal cortex of AD brains had higher histamine levels (Cacabelos et al., 1989). Nevertheless, other research has revealed reductions in histamine levels in AD brains' temporal cortex, hippocampus, and hypothalamus (Mazurkiewicz-Kwilecki andPanula et al., 1998; Nsonwah, 1989) [8].

Only the tuberomammillary nucleus (TMN) of the posterior hypothalamus contains histaminergic cell bodies (Brown et al., 2001). The location and quantity of histaminergic cell bodies were remarkably similar to those of normal brains, despite some findings indicating the presence of neurofibrillary tangles in the TMN of AD patients (Airaksinen et al., 1991). However, in the TMN, where several neurofibrillary tangles were discovered, indicating a central histaminergic malfunction, a different study demonstrated a considerable drop in large-sized histamine-containing neurons (Nakamura et al., 1993). Additionally, high histamine levels have been observed in the serum and cerebrospinal fluid of AD patients; however, mast cells may potentially be the source of this histamine (CNS) (Novoa Fernández andAccapello (2001). Four G-protein-coupled

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7-transmembrane receptor subtypes—H1, H2, H3, and H4—mediate the physiological effects of histamine (Brown et al., 2001; nomenclature follows Alexander et al., 2008). The subtypes of histamine receptors in AD brains have not been extensively studied [9].

While the number of H2 receptors in the temporal cortex and striatum has been found to be normal in AD post-mortem brains, a positron emission tomography investigation has shown a decrease in frontal and temporal H1 receptors in AD patients (Higuchi et al., 2000). (Perry et al., 1998). While there have been no publications to far identifying H4 receptors in AD brain, we recently provided preliminary evidence for qualitatively normal H3 receptor binding in AD medial temporal cortex (Medhurst et al., 2007). In relation to histamine receptors Specifically, H3 receptors are crucial for central nervous system regulation. While H3 heteroreceptor activation can inhibit the release of other neurotransmitters like acetylcholine, noradrenaline, dopamine, and 5-HT from non-histaminergic neurons, H3 auto receptor activation can inhibit the synthesis and release of histamine from histaminergic neurons (Arrang et al., 1983). On the other hand, selective antagonists that block H3 receptors can increase the release of neurotransmitters that are important in cognitive functions (Fox et al., 2005; Medhurst et al., 2007) [10].

In a variety of rodent cognition tests, selective H3 receptor antagonists have been demonstrated to enhance performance (Hancock and Fox, 2004; Witkin and Nelson, 2004; Medhurst et al., 2007). They have also been found to promote alertness (Brown et al., 2001; In 2004, Barbier et al. H3 receptor antagonists have been developed as a result, with the goal of treating many CNS illnesses, including cognitive dysfunction in AD (Passani et al., 2004; Esbenshade et al., 2008). A new and highly specific H3 receptor antagonist called GSK189254 has demonstrated effectiveness in several rat cognitive paradigms (Medhurst et al., 2007). In light of the scant literature on H3 receptors in AD, we used [3H]GSK189254 to study H3 receptor binding in the double mutant APPswe ¥ PSI. MI46V (TASTPM) transgenic mouse model of AD. These mice exhibit b-amyloid (Ab) accumulation from 3 months of age and cognitive impairments from 6 to 8 months of age due to over-expression of both the presenilin-1 (PS1.M146V) and human amyloid precursor protein (hAPP695swe) transgenes (Howlett et al., 2004). Within Additionally, we used autoradiography and saturation binding experiments to conduct a thorough investigation of H3 receptor binding with [3H]GSK189254 in human postmortem AD neocortex tissues. Since that H3 receptor antagonists are being investigated as a potential new symptomatic treatment for AD, these investigations show that H3 receptor integrity is maintained even in cases of severe AD. Techniques Transgenic mice with TASTPM Under the authority granted in personal and project licenses, all experimental procedures were carried out in accordance with the Home Office Guidance on the operation of the Animals (Scientific Procedures) Act 1986.

The GlaxoSmithKline Procedures Review panel reviewed and approved the procedures. Throughout, appropriate steps were taken to reduce any pain or suffering. Transgenic mice carrying presenilin-1 cDNAs and overexpressing human amyloid precursor protein were created using TASTPM. According to earlier descriptions, the swedish and M146V mutations, respectively, were produced (Richardson et al., 2003; Howlett et al., 2004). For saturation binding (n = 5 per group) and autoradiography (n = 6-8 per group) experiments, respectively, 13- or 16-month-old wild type (WT) and TASTPM mice were employed; at this ages, a considerable cognitive deficit and Ab burden would have been present for more than six months (Howlett et al., 2004). Brain tissues of humans After informed patient consent, local ethics committee approval, approval from GlaxoSmithKline human tissue committees, and approval from the Netherlands Brain Bank, human medial frontal gyrus tissues of varying disease severity (AD Braak stages I, II, IV, V, and VI; Braak and Braak (1991), male or female, ages 72-90 years, non-neurological cause of death) were obtained for autoradiography studies. Adherence to the Human Tissue Act of 2006.

As previously mentioned, twenty millimeter frozen sections were made (Roberts et al., 2004). Using a monoclonal 1E8 antibody (1: 1000 dilution) produced against the 13-27 fragment of Ab, as previously described (Howlett et al., 2004), AD plaque pathology was validated in neighboring sections. Tissues from a well-characterized cohort of AD patients with long-term follow-up in the community were employed for saturation binding investigations (Hope et al., 1997; 1999). From the time of study enrollment until death (a mean follow-up of 3.5 years), cognitive performance was evaluated every four months using the Mini-Mental State Examination (MMSE, scores 0-30, Folstein et al., 1975). Prior to the removal of the brain, tissues from the frontal (orbitofrontal gyrus, Brodmann area 11) and temporal regions were removed with the next of kin's informed agreement. The cortices of a maximum of 27 AD patients and 12 non-neurological controls were dissected, homogenized, and kept at-75°C as previously described (mid-temporal gyrus, Brodmann area 21) (Lai et al., 2003). Not all subjects had access to tissues from both regions; Table 1 lists the n values for each experiment. In this cohort, all samples were from severe AD (Braak V-VI). Autoradiography of the H3 receptor Based on earlier techniques, autoradiography studies were conducted (Roberts et al., 2004; Medhurst et al., 2007). Alzheimer's disease AD and twenty histamine H3 receptors British Journal 131: Medhurst et al.

Frozen slices of the brains of TASTPM or WT mice, or the human medial frontal gyrus, were thawed and placed on gelatin-coated slides. These were then kept at-80°C until the assay was conducted. Sections were incubated for 60 minutes at room temperature (22°C) in assay buffer, which contained 1 nmol·L-1 [3H]GSK189254 (50 mmol·L-1 Tris-HCl, pH 7.7 and 5 mmol·L-1 ethylenediaminetetraacetic acid (EDTA)). Non-specific binding was found on physically nearby areas when 10 mmol·L-1 imetit was present. All sections were rinsed five times for three minutes at 4°C in Tris-HCl solution after incubation, and 5 mmol·L-1 MgCl2 was added each time. After immediately dipping the sections in 4°C distilled water to eliminate buffer salts, they were dried in a cool air stream. After drying, the slices underwent digital autoradiography analysis utilizingAn instrument called Beta-Imager 2000 (Biospace, Paris, France). To aid with anatomical orientation, adjacent slices were additionally stained with cresyl fast violet. Using a monoclonal 1E8 (1: 1000) antibody produced against the 13-27 fragment of Ab, as previously described (Howlett et al., 2004), amyloid plaque pathology was validated in neighboring sections. Based on previously published techniques employing [3H]GSK189254, in vitro H3 receptor saturation binding and H3 receptor binding in WT and TASTPM mouse brains were ascertained (Medhurst et al., 2007). To prepare the membranes, a polytron P10 (2 ¥ 10 s bursts) was used to homogenize the tissue from the mouse entire brain (~13-month-old TASTPM and age-matched WT control) by resuspending 1 g of tissue to 10 mL in 50 mmol·L-1 Tris-HCl, 140 mmol·L-1 NaCl, and 1 mmol·L-1 EDTA buffer (pH 7.4 at 4°C). at maximum speed). The homogenate was spun for 20 minutes at 4°C using an SS34 rotor at a weight of around 48 000¥g in a Sorval Evolution RC centrifuge. The pellet was centrifuged once more after being cleaned with water and resuspended in assay buffer (50 mmol·L-1 Tris-HCl, pH 7.4). After being resuspended in assay buffer, the final cell pellet was frozen at-80°C until needed. [3H]

GSK189254 (20 nmol·L-1-0.02 nmol·L-1) and membranes (about 20 mg of protein per well) were incubated in polypropylene tubes with a final volume of 200 mL of 50 mmol·L-1 Tris-HCl, pH 7.7, at 25°C with 5 mmol·L-1 EDTA. It was found that non-specific binding occurred when 10 mmol·L-1 Imetit was present. For 45 minutes, reactions were carried out at 30°C. The tests were stopped quickly by filtering. after being presoaked in 0.3% (v/v) polyethyleneimine (PEI) and passed through Whatman GF/B filters (Whatman, Maidstone, UK). 4 ¥ 2 mL aliquots of ice-cold buffer containing 5 mmol·L-1 MgCl2 and 50 mmol·L-1 Tris-HCl, pH 7.7, at 25°C, were used to wash the filters. After drying, filters were put to vials holding 4 ml of Hewlett Packard's Ultima Gold MV scintillation fluid (Palo Alto, CA, USA). Using a Packard Tri-Carb 2500TR liquid scintillation counter (PerkinElmer Life and Analytical sciences, Boston, MA, USA), radioactivity was measured by liquid scintillation spectrometry. Using bovine serum albumin as a reference, protein concentrations were measured using the Bradford assay method (Bio-Rad protein assay Kit; Bio-Rad, York, UK). Aliquots of frozen brain homogenates were thawed, diluted in assay buffer (50 mmol·L-1 Tris-HCl, pH 7.4) and used for human AD investigations. added to six [3H]GSK189254 concentrations (0.05-5 nmol·L-1) in triplicate and left for two hours at 25°C. Ten millimol·L-1 unlabelled thioperamide maleate was added to a series of assay tubes in parallel to identify non-specific binding, which accounted for less than 10% of total binding. Protein was measured using an aliquot of the diluted homogenate and the Coomasie blue technique (Pierce Biotech Inc., Rockford, IL, USA). The experiment was stopped by quickly filtering ice-cold sodium phosphate buffer through 0.1% PEI-treated GF/B glass fiber filters (Whatman BDS, Maidstone, UK) in a cell harvester (Molecular Devices Ltd., Sunnyvale, CA, USA). After the filters were dried, membrane-bound radioactivity was assessed using a Wallac Beta counter and liquid scintillation spectrometry. Analysis of data Regarding autoradiography investigations in WT and TASTPM mice, [3H]GSK189254The amount of binding in the cortex, hippocampus, and hypothalamus was assessed using six measurements per region and five sections per animal. This was previously found to be the number of parts with statistical validation. A repeated measures ANOVA approach was used to analyze the data, and Statistica v6.0 StatSoft Inc. software was used. The levels of specific bound radioactivity were determined using the Betaimager by counting the number of beta particles from delineated areas. The results are expressed as mean specific binding counts per minute per square millimeter (cpm·mm-2; n = 6-8 animals per group). Using the Beta-imager, the amounts of particular bound radioactivity in the different brain regions of the human brain were ascertained by measuring the number of beta particles from defined whole section areas (defined as areas within the range ofradioligand binding signal was expressed as counts per minute per section (cpm per section) for each Braak stage, and the range of values was 86-252 mm2 across all sections (measured with a mean defined section area of 155.60 mm2). GraphPad Prism 3.0 by GraphPad Software Inc. (San Diego, CA, USA) was used to analyze specific binding in order to determine the binding parameters Bmax (total number of binding sites) and KD (binding affinity) for saturation binding tests in TASTPM and WT mice. EBDA and LIGAND software were used to perform the Scatchard transformation of data for human AD brain saturation binding tests utilizing [3H]GSK189254. (McPherson, 1985) to calculate

(McPherson, 1985) in order to determine Bmax and KD. As previously mentioned (Lai et al., 2003; 2005), dementia severity (mean of the final five MMSE scores prior to death, or MMSE5) was associated with Bmax using Pearson's product moment. In every instance, single sites with Hill coefficients (NH) close to one were the best candidates for binding isotherm fitting. Substances [3H]GSK189254 (6-[benzazepin-7-yl)oxy](3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-) Through a contract with GE Healthcare, UK,-N-methyl-3-pyridinecarboxamide hydrochloride (specific activity 81 Ci·mmol-1) was created. The suppliers of imetit and thioperamide maleate were Tocris Cookson Inc. (Bristol, UK). The remaining chemicals were of the reagent grade and were acquired from either Sigma-Aldrich Co. (St Louis, MO) or Invitrogen (Paisley, UK). Outcomes TASTPM rodents Coronal brain slices from a 16-month-old WT were auto radiographically analyzed (i) additionally In the cerebral cortex, hippocampus, and hypothalamus, TASTPM (ii) animals demonstrated significant specific [3H]GSK189254 binding (>80%), whereas binding levels were minimal after co-incubation with 10 mmol·L-1 imetit to define non-specific binding (iii). When compared to the absence of plaques in WT mice (iv), the presence of amyloid plaques in TASTPM animals (v) indicated a considerable amyloid load. The quantification of H3 receptor binding in the cortex, hippocampus, and hypothalamus of WT and TASTPM mice (n = 6-8 per group) did not show any significant changes. Using [3H]GSK189254, saturation binding was performed on entire brain membranes from 13-month-old WT and TASTPM mice. Over 90% of the overall binding was specific binding. In both WT and TASTPM mice, saturation analysis with [3H]GSK189254 produced Bmax values of 428 64 and 455. KD values of 0.4 0.02 and 0.33 ~ 0.04 nmol·L-1, respectively, and 104 fmol·mg-1 protein, respectively), with no significant differences between the groups found ($P > 0.05$, Student's t-test). Sections of the medial frontal AD cortex from Braak stages 0-1, II, IV, V, and VI showed >75% binding of the human AD brain H3 receptor autoradiography specific [3H]GSK189254. Adjacent sections stained with the 1E8 antibody to total Ab similarly showed plaque pathology. However, due to the small number of brains in this cohort, quantitative comparisons of H3 receptor binding in AD versus control brains were limited. At every stage of the disease, available, selective H3 receptor binding was evidently saturable. Human AD brain saturation binding of H3 receptors Additionally, using [3H]GSK189254 saturation tests, we quantitatively analyzed H3 receptor binding in a broader cohort of AD and normal brains A displays a typical plot of binding data from the AD frontal cortex. At radioligand doses close to KD, full saturation of binding was attained, and [3H]GSK189254 binding had a high specificity (>90% total). Table 1 displays the average frontal and temporal cortex H3 receptor binding values as well as demographic information from both AD patients and controls. There were no variations in [3H]GSK189254 binding between AD cases and controls, despite the age and post-mortem intervals being matched. parameters (Student's t-test, $P > 0.05$) between the two groups. Fascinatingly, frontal cortical [3H]GSK189254 Bmax within the AD group had a negative correlation with the average of the final five MMSE scores prior to death. In order to prevent floor effects related to protracted terminal states commonly observed in AD, MMSE5, as opposed to predeath MMSE, was utilized as an indication of dementia severity (Lai et al., 2003). Consequently, [3H]GSK189254 binding density was higher in the AD group among those who had more severe dementia (lower MMSE5) before passing away. The temporal cortex, however, did not show this connection.

Conversation

In this work, we have demonstrated that, in both the human AD brain and the transgenic mice overexpressing TASTPM relative to WT mice, H3 receptor binding is not significantly changed. Considering that H3 receptor antagonists are presently being explored as a potential strategy for the symptomatic treatment of AD, these data demonstrating the persistence of H3 receptors even in late stage AD are significant.

One of the main features of AD and associated dementias is progressive cognitive decline, and improving cognitive function in these conditions is a difficult task because multiple brain regions and neurotransmitter systems are involved (Corey-Bloom, 2002). The benefit of current treatments, including cholinesterase inhibitors, is only marginally beneficial to a small percentage of patients and only temporarily. Thus, several other approaches to treating symptoms are being investigated, such as the creation of selective histamine H3 receptor antagonists (Johnson et al., 2004). It is commonly known that via a pre-synaptic inhibitory mechanism, H3 receptors can regulate the release of certain neurotransmitters involved in cognitive functions (Blandina et al., 1996; Fox et al., 2005). Structurally diverse non-imidazole H3 antagonists, such as GSK189254, ABT-239, and BF2.649, have been demonstrated to block this feedback loop and, in line with blockade of H3 heteroreceptors, increase the release of several neurotransmitters in the cortex, including dopamine and acetylcholine (Fox et al., 2005; Ligneau et al., 2007; Medhurst et al., 2007; Esbenshade et al., 2008). Furthermore, numerous H3 receptor antagonists' beneficial benefits have been documented in a vast a variety of rodent cognition paradigms that incorporate various brain substrates, learning and memory processes, and other elements. These have been well addressed before, and most research indicates that H3 receptor antagonists have pro-cognitive effects (Witkin and Nelson, 2004; Esbenshade et al., 2008). For instance, when administered abruptly or frequently, GSK189254 demonstrates effectiveness in a variety of rat cognition models, including the water maze, novel object recognition paradigms, attentional set shift, and passive avoidance (Medhurst et al., 2007). H3 receptor antagonists are an appealing therapeutic option for a variety of CNS illnesses, including Alzheimer's disease (AD), various dementias, and cognitive dysfunction in schizophrenia, due to their effects on several neurotransmitters and pro-cognitive benefits (Passani et al., 2004). Considering the curiosity about the possible development We were interested in finding the integrity of H3 receptors in human post-mortem AD brains and in a transgenic mouse model of AD in order to evaluate the efficacy of H3 receptor antagonists for AD. Although its affinity for the rat H3 receptor is approximately ten times lower than that of the human receptor, we have previously demonstrated that [3H]GSK189254 is a good radioligand for examining H3 receptor binding in both rat and human brain (Medhurst et al., 2007). Rat striatal, cortical, thalamic, hippocampus, and hypothalamic areas as well as the substantia nigra showed dense specific binding, while white matter areas showed low binding. These findings are similar with prior studies that used different H3 receptor radioligands (Pollard et al., 1993; Barbier et al., 2004). In the present investigation, we noted a comparable binding affinity. and distribution pattern in the mouse brain as opposed to the rat brain, with the hippocampus, hypothalamus, and cerebral cortex showing a disproportionate amount of H3 receptor binding. Despite a notable amyloid load in the cerebral areas of TASTPM mice at 13-16 months of age, no variations in H3 receptor density were found between TASTPM and WT animals using either autoradiography or saturation binding studies in homogenates. We did not look into any potential association between H3 receptor expression and severity of cognitive deficiency, as we did with the MMSE5 in human AD brains, because it was previously impossible to discern between degrees of cognitive deficit in these mice (Howlett et al., 2004). But even if there are notable amyloidosis and cognitive abnormalities (as assessed by the object recognition paradigm) in According to this concept (Howlett et al., 2004; 2008), neurodegeneration is not a significant pathogenic component, which could explain why the current study's findings on neuronal H3 receptors showed no changes. Therefore, as neurodegeneration would have undoubtedly occurred in human AD brains, we also looked into H3 receptor binding in these brains. [H3]According to other studies (Martinez-Mir et al., 1990; Anichtchik et al., 2001), GSK189254 has been demonstrated to label specific H3 receptor binding sites in human control and AD medial temporal cortex. The localization appears consistent with a neuronal localization (Medhurst et al., 2007). In the current work, we expanded these initial findings to the same people's medial frontal cortex, as well as to another extremely well-characterized cohort of AD and control medial and temporal According to this concept (Howlett et al., 2004; 2008), neurodegeneration is not a significant pathogenic component, which could explain why the current study's findings on neuronal H3 receptors showed no changes. Therefore, as neurodegeneration would have undoubtedly occurred in human AD brains, we also looked into H3 receptor binding in these brains. [H3]According to other studies (Martinez-Mir et al., 1990; Anichtchik et al., 2001), GSK189254 has been demonstrated to label specific H3 receptor binding sites in human control and AD medial temporal cortex. The localization appears consistent with a neuronal localization (Medhurst et al., 2007). In the current work, we expanded these initial findings to the same people's medial frontal cortex, as well as to another extremely well-characterized cohort of AD and control medial and temporal samples of cortex that have been previously reported (Hope et al., 1997; 1999). Specific H3 receptor binding was detected in medial frontal cortical samples of AD patients with Braak stages I, II, IV, V, and VI using autoradiography. These results were consistent with our earlier findings that the same individuals' medial temporal cortex exhibited H3 receptor binding. This suggests that H3 receptor expression is widespread throughout the course of the disease, including in severe cases, within two cortical areas that are primarily affected by AD pathology. Saturable binding in each individual participant appeared comparable across the several Braak phases, but regrettably, the small sample size available precluded a significant quantitative comparison in this cohort of AD brains compared with controls. Still, we were possible to measure [3H] GSK189254 binding using control brains that have more precise clinical data regarding the severity of the disease in terms of cognitive function and cortical homogenates from a larger cohort of AD patients (Braak V-VI). In line with earlier findings of species variations in pharmacology between human and rat H3 receptors, the KD for [3H] GSK189254 in human brain was around ten times lower than that seen in TASTPM and WT mice (Medhurst et al., 2007). The [3H]GSK189254 binding levels in the control and AD neocortex were modest (Bmax ~ 10-15 fmol·mg-1) and did not differ substantially between the two groups. This is in line with the autoradiography experiments conducted in the smaller cohort that was previously published. This implies that although H3 receptors might not be directly related to AD, they might become important as a neurotransmitter system negative modulator. particularly those that are impaired by serious illness, aggravating the deficiencies. Although autoreceptors on histaminergic neurons may also exist, the majority of cortical H3 receptors are thought to be heteroreceptors on intrinsic neurons mediating cholinergic and monoaminergic function (Cumming et al., 1991; Pollard et al., 1993; Blandina et al., 1996; Fox et al., 2005). Thus, insofar as cholinergic and monoaminergic neurotransmitter systems mediate these cognitive functions, an H3 receptor antagonist may be able to mitigate neurotransmitter shortage and enhance cognition. Interestingly, frontal cortex [3H]GSK189254 binding density within the AD group looked higher in individuals with more severe dementia prior to death (based on MMSE5), yet there were no differences between AD and normal brains. In the temporal cortex, this was not the case. It is challenging to understand why frontal cortex has increased H3 receptor binding. Though a drop in these receptors is also shown in the temporal

cortex, it is possible that it is a compensatory strategy to offset alterations in the histaminergic system elsewhere in severe AD, such as a decrease in frontal cortex H1 receptors (Higuchi et al., 2000). Furthermore, an increase in H3 receptor density may have the functional consequence of further depleting cognitive neurotransmitters, which would exacerbate cognitive deficiencies and prevent any favorable compensating impact. Alternatively, the loss of cholinergic neurons may be the only explanation for the increased H3 receptor binding observed in the brains of patients with more advanced dementia. The cause of It's also unclear how the frontal and temporal cortex differ regionally, however this could be due to variations in AD pathology in various cortical regions. There are two possible explanations for this: either the H3 receptor's function varies depending on the region, or the early selective degeneration of the temporal lobe in comparison to the frontal cortex has reached a nadir, making it impossible to activate the systems that the H3 receptor regulates (such as acetylcholine and monoamines) (Wilcock and Esiri, 1987; Scahill et al., 2002). Nevertheless, additional research is necessary to investigate this possible difference in a larger cohort of AD and control brains because to the relatively small sample size. This is the first quantitative study evaluating the H3 receptor that we are aware of. brains of AD with binding density. H3 receptor binding was either enhanced or remained unaltered in studies using brains from other neurodegenerative disorders, such as Parkinson's disease (Anichtchik et al., 2001), emphasizing the value of examining other cohorts. The observation of H3 binding in cases of severe dementia in both of our cohorts supports the notion that H3 receptors appear to be relatively spared in AD and may be therapeutically blocked by H3 antagonists. Although there isn't much of a difference in H3 receptor binding between AD and control brains, our findings don't tell us anything about how receptor coupling or other downstream processes are impacted. H3 receptor antagonists, for instance, have been shown to enhance the release of a variety of neurotransmitters (Schlicker et al., 1994; Blandina et al., 1996). If there were variations in the density of other receptors controlling the reactions to the increased neurotransmitters produced after H3 receptor inhibition, the consequences of this possible therapeutic intervention in AD might be controlled. To determine whether processes that are downstream of the H3 receptor are impacted in AD and may lead to distinct reactions to H3 receptor antagonists than in healthy persons, more thorough research is necessary. In conclusion, we have demonstrated that H3 receptor binding was identical to WT mice in the TASTPM mouse model of AD, which exhibits a substantial Ab plaque load. Furthermore, we have statistically and qualitatively shown that H3 receptor binding is maintained across the various Braak stages of AD and does not seem to differ appreciably in AD brains from controls matched by age. Given the potential use of H3 antagonists as a novel therapeutic approach for the symptomatic treatment of various diseases, this preservation of H3 receptor integrity is critical.

References

1. Hancock AA, Fox GB (2004) Perspectives on cognitive domains, H3 receptor ligands and neurological disease. Expert Opin Investig Drugs 13: 1237-1248.
2. Higuchi M, Yanai K, Okamura N, Meguro K, Arai H, Itoh M et al. (2000) Histamine H(1) receptors in patients with Alzheimer's disease assessed by positron emission tomography. Neuroscience 99: 721-729.
3. Hope T, Keene J, Gedling K, Cooper S, Fairburn C, Jacoby R (1997) Behaviour changes in dementia. 1: point of entry data of a prospective study. Int J Geriatr Psychiatry 12: 1062-1073.
4. Hope T, Keene J, Fairburn CG, Jacoby R, McShane R (1999) Natural history of behavioural changes and psychiatric symptoms in Alzheimer's disease, a longitudinal study. Br J Psychiatry 174: 39-44.
5. Howlett DR, Richardson JC, Austin A, Parsons AA, Bate ST, Davies DC et al. (2004) Cognitive correlates of Abeta deposition in male and female mice bearing amyloid precursor protein and presenilin-1 mutant transgenes. Brain Res 1017: 130-136.
6. Howlett DR, Bowler K, Soden PE, Riddell D, Davis JB, Richardson JC et al. (2008) Abeta deposition and related pathology in an APP ¥ PS1 transgenic mouse model of Alzheimer's disease. Histol Histopathol 23: 67-76.
7. Johnson CN, Roland A, Upton N (2004) New symptomatic strategies in Alzheimer's disease. Drug Discov Today Ther Strateg 1: 13-19.
8. Lai MK, Tsang SW, Francis PT, Esiri MM, Keene J, Hope T et al. (2003) Reduced serotonin 5-HT1A receptor binding in the temporal cortex correlates with aggressive behavior in Alzheimer disease. Brain Res 974: 82-87.
9. Lai MK, Tsang SW, Alder JT, Keene J, Hope T, Esiri MM et al. (2005) Loss of serotonin 5-HT2A receptors in the postmortem temporal cortex correlates with rate of cognitive decline in Alzheimer's disease. Psychopharmacology (Berl) 179: 673-677.
10. Ligneau X, Perrin D, Landais L, Camelin JC, Calmels TP, Berrebi-Bertrand I et al. (2007) BF2.649 [1-{3-[3-(4-Chlorophenyl) propoxy]propyl}piperidine, hydrochloride], a nonimidazole inverse agonist/antagonist at the human histamine H3 receptor: Preclinical pharmacology. J Pharmacol Exp Ther 320: 365-375.