5-HT\textsubscript{2A} and 5-HT\textsubscript{2C} receptor polymorphisms and psychopathology in late onset Alzheimer’s disease

Clive Holmes\textsuperscript{1,2,*}, Maria J. Arranz\textsuperscript{3}, John F. Powell\textsuperscript{2}, David A. Collier\textsuperscript{4} and Simon Lovestone\textsuperscript{1,2}

\textsuperscript{1}Section of Old Age Psychiatry, \textsuperscript{2}Department of Neuroscience, \textsuperscript{3}Department of Psychological Medicine and \textsuperscript{4}Department of Psychological Medicine and Neuropathology, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK

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The psychopathology of Alzheimer’s disease (AD) is varied and includes both behavioural and psychological symptoms. Behavioural and psychological symptoms are common and contribute to the difficulties experienced by carers. However, the mechanism whereby these symptoms occur in some individuals with AD is not understood. We hypothesized that common genetic polymorphisms in neurotransmitter systems are risk factors for these symptoms in the course of AD. A total of 211 subjects from a population-based prospective study of psychopathology within late-onset AD were genotyped for the 5-HT\textsubscript{2A} receptor polymorphism 102-T/C and the 5-HT\textsubscript{2C} receptor polymorphism Cys23Ser. Associations were found between the presence of the C102 allele and the presence of visual (Fisher’s exact test, one-tailed, \( P = 0.003 \)) and auditory hallucinations (Fisher’s exact test, one-tailed, \( P = 0.004 \)) and between the presence of the Ser23 allele and visual hallucinations (\( \chi^2 = 7.5, \text{df} = 1, P = 0.006 \) (\( P = 0.03, 0.04 \) and 0.06, respectively, after Bonferroni correction). In addition, there was an association between the Cys23Ser polymorphism and hyperphagia (\( \chi^2 = 6.7, \text{df} = 2, P = 0.03 \) (\( P = 0.3 \) after Bonferroni correction)). We conclude that common 5-HT\textsubscript{2A} and 5-HT\textsubscript{2C} genetic polymorphisms previously showing only weak associations with psychotic illness are associated with psychotic symptoms in AD but are clinically silent until the onset of the neurodegenerative process.

INTRODUCTION

Whilst, by definition (1,2), cognitive decline is invariably present in Alzheimer’s disease (AD), a variety of other symptoms are also present, with psychotic symptoms found in approximately one-third of cases (3,4). The mechanism whereby these neuropsychiatric complications occur in some individuals with AD is not understood, but may be related to selective loss of different neuronal populations (5) or specific neurotransmitters (6). An alternative hypothesis is that genetic risk factors for other psychiatric syndromes or variants in neurotransmitter systems are risk factors for psychopathology in the course of AD. We combined these hypotheses and predicted that common polymorphic variations in the 5-HT\textsubscript{2A} and 5-HT\textsubscript{2C} serotonin receptor genes (102-T/C and Cys23Ser polymorphisms, respectively) implicated previously in psychosis (7,8) would be associated with psychotic symptoms in AD. In addition, we looked at the possible associations of these polymorphisms with aggression, a symptom previously associated with 5-HT\textsubscript{2A} receptor loss in AD at post-mortem (9) and hyperphagia, a symptom observed in 5-HT\textsubscript{2C} receptor null mice (10).

RESULTS

Genotype frequencies for the 5-HT\textsubscript{2A} 102-T/C polymorphism did not differ significantly between the total AD group (16% for T102/T102, 55% for T102/C102 and 29% for C102/C102) and the controls (16, 51 and 33%, respectively; \( \chi^2 = 0.7, \text{df} = 2, P = \text{not significant} \)), and separate analysis by gender also showed no significant differences in genotype frequencies. Likewise, genotype frequencies for the X-linked 5-HT\textsubscript{2C} gene Cys23Ser polymorphism did not differ significantly between the female AD group (76% for Cys/Cys, 22% for Cys/Ser and 2% for Ser/Ser) and the female controls (79, 20 and 1%, respectively; \( \chi^2 = 0.8, \text{df} = 2, P = \text{not significant} \)) or between the male AD group (87% for Cys alone and 13% for Ser alone) and the male controls (87 and 13%, respectively; \( \chi^2 = 0.02, \text{df} = 1, P = \text{not significant} \)).

No significant associations were found between the presence of psychopathology with gender, duration of illness or past psychiatric illness, and no significant association was found between either polymorphism and the presence of delusions or aggression in AD subjects. Associations were found between the 102-T/C polymorphism and the presence of visual (\( \chi^2 = 8.3, \text{df} = 2, P = 0.015 \)) and auditory hallucinations (\( \chi^2 = 6.5, \text{df} = 2, P = 0.04 \)) for genotype frequencies (Table 1). Associations were also found for the total group between the Cys23Ser polymorphism and visual hallucinations (\( \chi^2 = 7.7, \text{df} = 2, P = 0.02 \)) and hyperphagia (\( \chi^2 = 6.7, \text{df} = 2, P = 0.03 \)) for genotype frequencies (Table 2).

*To whom correspondence should be addressed. Tel: 0171 919 3626; Fax: 0171 701 0167; Email: c.holmes@iop.bpmf.ac
Separate analysis by gender for the Cys23Ser polymorphism showed a non-significant trend for both females ($\chi^2 = 5.2, df = 2, P = 0.07$) and males ($\chi^2 = 3.4, df = 1, P = 0.07$) with visual hallucinations, and an association between hyperphagia and females ($\chi^2 = 7.6, df = 2, P = 0.02$) but not with males who are hemizygous for this gene ($\chi^2 = 0.6, df = 1, P = 0.48$) for genotype frequencies. Assuming the C102 and Ser23 alleles to be dominant increased the strength of the associations between the presence of the C102 allele and the presence of visual hallucinations [one-tailed Fisher’s exact test, $P = 0.003$; odds ratio (OR): 9.9; 95% confidence interval (CI): 1.3–77.6] and auditory hallucinations [one-tailed Fisher’s exact test, $P = 0.004$] and between the presence of the Ser23 allele and visual hallucinations ($\chi^2 = 7.5, df = 1, P = 0.006$; OR: 2.7; 95% CI: 1.3–5.7).

Table 1. Genotype frequencies of the T102C polymorphism in the 5-HT$_{2A}$ gene in AD subjects by presence or absence of psychopathology

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>5-HT$_{2A}$ receptor genotype frequencies (%)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>T102/T102</td>
<td>C102/T102</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present 43</td>
<td>30 (69.9)</td>
<td>12 (27.9)</td>
</tr>
<tr>
<td>Absent 168</td>
<td>86 (51.2)</td>
<td>50 (29.8)</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present 30</td>
<td>20 (66.7)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Absent 181</td>
<td>96 (53.1)</td>
<td>52 (28.7)</td>
</tr>
<tr>
<td>Delusions</td>
<td>66 (55.9)</td>
<td>33 (28.0)</td>
</tr>
<tr>
<td>Absent 93</td>
<td>50 (53.7)</td>
<td>29 (31.2)</td>
</tr>
<tr>
<td>Aggression</td>
<td>52 (55.9)</td>
<td>26 (28.0)</td>
</tr>
<tr>
<td>Absent 118</td>
<td>64 (54.2)</td>
<td>36 (30.5)</td>
</tr>
<tr>
<td>Hyperphagia</td>
<td>14 (48.3)</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td>Hyperphagia</td>
<td>102 (56.0)</td>
<td>52 (28.6)</td>
</tr>
<tr>
<td>All cases</td>
<td>116 (55.0)</td>
<td>62 (29.4)</td>
</tr>
</tbody>
</table>

*Presence of visual hallucinations relative to Cys23Ser genotype $\chi^2 = 7.7, df = 2, P = 0.006$ (total group, see text for gender differences) and to the presence of the Ser23 polymorphism $\chi^2 = 7.5, df = 1, P = 0.006$ (after Bonferroni correction).

**Presence of auditory hallucinations relative to Cys23Ser genotype $\chi^2 = 6.8, df = 2, P = 0.003$ (total group, see text for gender differences; $P = 0.3$ after Bonferroni correction).

Logistic regression analysis with the presence of visual hallucinations as the outcome variable showed no evidence of confounding between the presence of the C102 allele and the presence of the Ser23 allele. In addition, there was no evidence that the association between the presence of the C102 allele and the presence of visual and auditory hallucinations or the association between the presence of the Ser23 allele and visual hallucinations was confounded by duration of illness.

**DISCUSSION**

The major finding of this study is the strong association of both the 5-HT$_{2A}$ 102-T/C and 5-HT$_{2C}$ Cys23Ser polymorphisms with the presence of visual hallucinations in AD. Thus, of the 211 AD subjects studied, 28 subjects had neither the C102 or the Ser23 allele and none had visual hallucinations. Of the 142 subjects who had either the C102 or the Ser23 allele, 28 (19.7%) had visual hallucinations, and of the 41 subjects who had both the C102 and the Ser23 allele, 15 (36.6%) had visual hallucinations, suggesting an additive effect of the two polymorphisms. This data strongly support LSD-binding studies (11) suggesting a role for these receptors in sensory information processing.

In contrast to the 5-HT$_{2C}$ Ser23 allele, we found a strong association between the 5-HT$_{2A}$ C102 allele and the presence of both auditory and visual hallucinations, suggesting that these receptors show both distinct and overlapping functions. Auditory and visual hallucinations co-exist to variable degrees in different psychiatric conditions. AD has both auditory and visual hallucinations (4) while schizophrenia is characterized by auditory hallucinations and, to a much lesser degree, visual hallucinations (1). It might be anticipated that the weak association found between the presence of the 5-HT$_{2A}$ C102 allele and schizophrenia (7) would be strengthened if association was sought with the psychopathology of the disease rather than the diagnosis.
No association was found between aggressive behaviour and the presence of the 5-HT2A C102 allele, suggesting that either 5-HT2A receptor loss is not implicated in aggression in AD or that the 5-HT2A C102 allele is not associated with 5-HT2A receptor loss. A positive association was found between hyperphagia and the 5-HT2C Ser23 allele in female AD subjects, but the association was small and was non-significant after Bonferroni correction (12), suggesting that this finding should be explored in a larger sample. The lack of association between the 5-HT2A 102-T/C and the 5-HT2C Cys23Ser polymorphisms and AD suggests that neither polymorphism is a risk factor for AD but does not rule out a contribution of these polymorphisms to cognitive progression or non-cognitive symptomatology of the disease once initiated.

In summary, a number of symptoms in AD appear associated with both a 5-HT2A C102 allele and a 5-HT2C Ser23 allele. These positive associations, combined with a lack of association with risk for AD and with past psychiatric history, suggest that these genetic variations represent risk factors for psychotic experiences which are too weak to result in psychotic illness without some other factor being present, in this case neurodegeneration. Similar mechanisms have been postulated previously for familial psychosis with Huntington’s disease (13) and suggest new approaches in the difficult field of schizophrenia genetics. For AD, the possibility of screening for predictors of non-cognitive symptomatology, a major cause of carer burden and health service resource allocation, is raised for the first time.

MATERIALS AND METHODS

A total of 211 subjects (164 females and 49 males) with late-onset AD, as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS–ADRDA) (2) criteria, and not meeting research criteria for either the Consensus criteria for Dementia with Lewy Bodies (14) or the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement Neurosciences (NINDS–AIREN) (15) criteria were recruited from the Cambertwell Dementia Case Register (16). The subjects and the next-of-kin or main carer were interviewed in all cases and the presence of previous psychiatric history assessed by means of the CAMDEX (17). Presence of psychopathology was assessed by the Manchester and Oxford Universities Scale for the Psychological Assessment of Dementia (MOUSEPAD) (18).

AD subjects and 181 population controls were genotyped for the 5-HT2A receptor polymorphism 102-T/C and the 5-HT2C receptor polymorphism Cys23Ser. Genotyping of the 102-T/C polymorphism was by PCR amplification of DNA and digestion of the 372 bp product with MspI, which cuts the C102 allele only, giving 156 and 216 bp fragments (19). Similarly, genotyping of the Cys23Ser polymorphism was by PCR amplification of DNA and digestion of the 104 bp product with HinfII, which cuts the Ser23 allele only, giving 86 and 18 bp fragments (20). Restriction fragments were visualized by agarose gel electrophoresis followed by staining with ethidium bromide.

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REFERENCES