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Brief report

Serotonin-1A receptors in frontotemporal dementia compared with controls

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Abstract

Using PET neuroimaging, we demonstrated that four frontotemporal lobar dementia (FTLD) patients had significantly decreased serotonin 5-HT_{1A} binding potential (BP) compared with controls in all 10 brain regions examined. These pilot data suggest that profound 5-HT_{1A} BP losses may be present and contribute to symptomatology and treatment response in FTLD.

Keywords: Serotonergic system; Binding potential; PET imaging

1. Introduction

Frontotemporal lobar degeneration (FTLD) is a progressive dementia associated with selective atrophy of frontotemporal brain regions and relative sparing of posterior regions (Whitwell et al., 2004). While the etiology of FTLD remains to be elucidated, disruption of the serotonergic system appears to be important in the clinical manifestation of the disease (Franceschi et al., 2005; Lanctôt et al., 2001). The serotonin 5-HT_{1A} receptor is a key component of serotonergic regulation and plays a major role in modulating mood, anxiety, cognition, feeding and thermoregulation (Pucadyil et al., 2005). As the clinical manifestations of FTLD include prominent behavioral changes, such as apathy, inappropriate social behavior and disinhibition, in addition to cognitive symptoms such as executive dysfunction and language decline (Perry and Hodges, 2000), restoration of the serotonergic system could play an important role in the effective management of the disease (Franceschi et al., 2005). As such, it is important to characterize the precise nature of the changes to the serotonergic system that occur in this disease process.

2. Methods

Four FTLD patients meeting diagnostic criteria of the Report of the Work Group on frontotemporal dementia and Pick's Disease (3 behavioral and 1 language variant) were recruited for participation in this study. Subjects were excluded if they had abnormal biochemical screening, significant vascular risk factors (Hachinski

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ischemic score >3) or a brain MRI that revealed lesions not consistent with FTLD. Patients with significant medical illness, depressive symptoms (Cornell Scale for depression in dementia >8) or those on serotonergic medications were also excluded. The eight controls were recruited from the community, each with a Mini Mental Status Examination (MMSE) score greater than 26 (Crum et al., 1993). Neuropsychological testing confirmed that learning, memory, language, visuospatial function and executive function were within normal limits.

A GEMS-2048-15B PET scanner was used to generate PET images following a bolus injection of 10 mCi of [^{11}C]WAY-100635. The images were attenuation-corrected using a ^{68}Ge transmission scan and reconstructed using filtered back projection (Hanning filter, 5 mm full-width at half maximum), yielding 15 axial slices, each 6.5 mm thick. Subjects underwent an MRI scan on a GE Signa 1.5T scanner to obtain a T2/Proton-Density image using a fast spin-echo dual-echo sequence and T1 image using a fast spin-echo sequence. MRI scans were co-registered to the appropriate PET images using RView co-registration software (Studholme et al., 1999). 5-HT$_{1A}$ receptor binding was analyzed based on pre-defined regions of interest (ROIs) drawn manually on the co-registered MRI (Bremner et al., 1998). Decay-corrected time activity curves were generated for the first 60 min of the data acquisition period for each subject. Following Lammertsma's non-invasive Simplified Reference Tissue Model (Lammertsma and Hume, 1996) and using the cerebellum (relatively devoid of 5-HT$_{1A}$ receptors) as an area of reference, binding potential (BP) values were calculated for each ROI and corrected for partial volume effects due to atrophy using the method of Muller-Gartner (Muller-Gartner et al., 1992).

Atrophy-corrected 5-HT$_{1A}$ BP values were compared using multivariate analysis of variance (MANOVA) with diagnosis (FTLD or control) as the independent variable and the BPs from the ROIs as the dependent variables (SPSS for Windows, version 14.0). Between-subjects results were used to determine the contribution of each ROI to the overall difference between the groups. Demographic characteristics were compared by Fisher exact test for gender and *t*-tests, adjusted for unequal variances if necessary, for age and years of education.

3. Results

Groups were comparable for gender, age and years of education. The mean (±S.D.) ages of the FTLD and control subjects were 63.0±6.7 and 69.0±7.5, respectively (P=0.21) , and the mean (±S.D.) years of education for the two groups were 16.3±2.9 and 14.9±2.9, respectively (P=0.26). There were two males and two females in the FTLD group and five males and three females in the control group (P=0.99). The average MMSE scores were 14.5 (±8.3) in the FTLD group and 28.8 (±0.7) in the control group (P=0.04).

The FTLD group had been diagnosed on average 2 (±1.4) years ago, and the patients were mild to moderate on the Global Deterioration Scale (4.8±0.1). Concomitant medications in the FTLD group were donepezil (n=2), enalapril (n=1) and supplements (phosphatidylserine n=1, antioxidants n=1, vitamins n=1, gingko n=1), while concomitant medications in the control

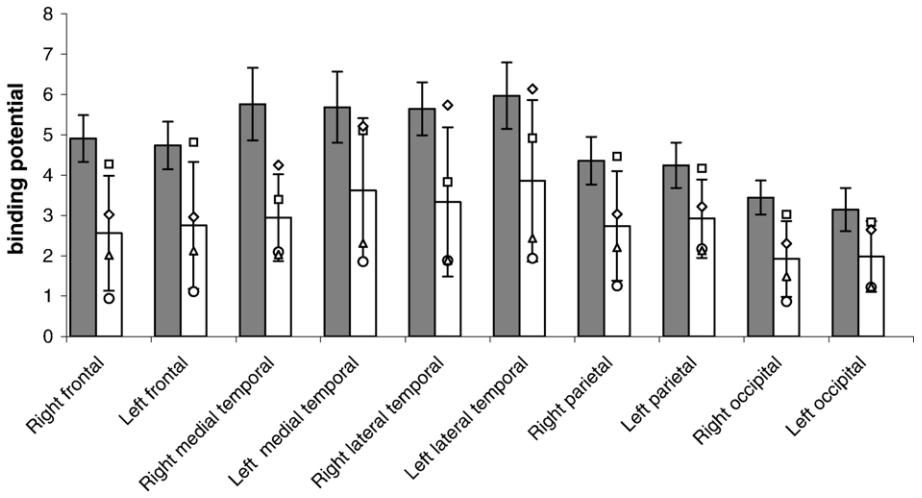

Fig. 1. Atrophy adjusted binding potential for FTLD patients versus controls. The gray column represents the mean (S.D.) for the controls; the white column represents the mean (S.D.) for the FTLD. The points represent the 4 FTLD subjects (one with language variant (diamond)).

group were celecoxib ($n=2$), terazosin ($n=1$), ASA ($n=1$) and supplements (vitamin E $n=2$, vitamin C $n=2$, calcium $n=1$ and CoQ_{10} $n=1$).

Significant decreases in BP were widely demonstrated in the FTLD patients compared with the controls. On average, FTLD patients had BPs that were 63% of control BPs. After controlling for atrophy, FTLD BP values ranged from 50% to 69% of control BP values. MANOVA showed significant differences by diagnosis ($F_{1,10}=379$, $P=0.04$). Post-hoc tests evaluating between-subject effects showed that 5-HT_{1A} BP values of FTLD patients were significantly lower than those of controls in all 10 ROIs (Fig. 1) namely: frontal ($P=0.009$ left and 0.002 right), medial temporal ($P=0.021$ left and 0.001 right), lateral temporal ($P=0.024$ left and 0.008 right), parietal ($P=0.013$ left and 0.014 right) and occipital ($P=0.016$ left and 0.003 right) regions.

MANOVA showed significant differences in percentage of grey matter by diagnosis ($F_{1,9}=511$, $P=0.03$) with tests of between-subjects effects showing that FTLD patients had significantly less grey matter than controls in all ROIs except the left and right occipital ($P=0.86$, $P=0.72$), right parietal ($P=0.13$) and left medial temporal lobes ($P=0.08$). There was no significant difference in cerebellar [^{11}C]WAY-100635 uptake ($P=0.37$). ROI volumes were not significantly different between the groups ($P=0.14$).

4. Discussion

This pilot study demonstrates that 5-HT_{1A} receptor BP is significantly decreased in FTLD patients compared with healthy normal controls. Previously, post-mortem studies demonstrated loss of 5-HT_{1A} and 5-HT_{2A} receptor expression in FTLD, and a recent PET study demonstrated decreased 5-HT_{2A} receptor BP in FTLD (Huey et al., 2006). While the magnitude of differences in BP was greatest in frontal and temporal regions mirroring expected FTLD pathology (Whitwell et al., 2004), our findings support a global loss of 5-HT_{1A} receptors. With behavioral changes predominating early in FTLD rather than memory changes as seen in early Alzheimer's disease (Franceschi et al., 2005), it is not surprising that the profile of neurotransmitter and receptor changes in FTLD would differ from that of other dementing processes. Results in Alzheimer's disease demonstrate that significant loss of 5-HT_{1A} receptors is limited to the right medial temporal region in the mild to moderate stages (Lanctôt et al., 2007). Our results provide evidence that serotonergic changes may be important in the clinical presentation of FTLD (Huey et al., 2006).

Our findings could have important treatment implications. It has been proposed that 5-HT_{1A} antagonists could enhance cognition in dementia as activation of post-synaptic 5-HT_{1A} in the hippocampus has a negative effect on memory retention. With BPs of 5-HT_{1A} decreased to the extent that we observed in FTLD patients, treatment modalities blocking this receptor may not be rational. Second, treatment response to serotonin reuptake inhibitors and atypical antipsychotics involves stimulation of 5-HT_{1A} receptors. Our findings suggest that efficacy may be limited due to widespread cortical loss of 5-HT_{1A} receptors.

The small sample size must be considered in the interpretation of these results. A definitive statement regarding 5-HT_{1A} BP differences in FTLD compared with normal subjects must await replication of these results in a larger sample size. Nevertheless, these preliminary findings suggest that a larger study is warranted.

In summary, this study demonstrated that 5-HT_{1A} BP was profoundly reduced in all brain regions examined in a small sample of patients with FTLD compared with healthy elderly controls. While BP does not directly measure receptor function, ongoing loss of receptors might be expected to have a corresponding impact on function. 5-HT_{1A} plays a critical role in cognitive and non-cognitive functions, and its loss could be an important factor in the pathophysiology of FTLD. These findings have important treatment implications as loss of 5-HT_{1A} potentially limits the use of pharmacologic agents that require this receptor.

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