A serotoninergic basis for hyperphagic eating changes in Alzheimer's disease

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A B S T R A C T

Hyperphagia and associated eating changes occur frequently in Alzheimer's disease (AD) and lead to considerable morbidity. However, the neurochemical basis for these neuropsychiatric behaviours is at present unclear. In this study, we measured serotonin transporters, 5-HT 1A, 5-HT 2A, and 5-HT 4 receptors using radioligand binding assays in the postmortem temporal cortex of a cohort of controls and AD patients longitudinally assessed for hyperphagia. We found significant decreases in 5-HT 4 receptor densities in the hyperphagic, but not normophagic, AD group. Our data suggest that 5-HT 4 receptor deficits may be a specific neurochemical correlate of hyperphagia, and point to the potential pharmacotherapeutic utility of 5-HT 4 agonists for these behaviours in AD.

1. Introduction

Neuropsychiatric and non-cognitive behaviours occur frequently in elderly patients with Alzheimer’s disease (AD), and are a major source of distress to caregivers, often precipitating institutionalization of the patient [1–4]. Of these behaviours, various forms of eating changes including overeating (hyperphagia) have been reported to occur in 10–36% of AD patients [5–8]. Without caregiver intervention, people with dementia who develop hyperphagia will continue eating until they seem physically uncomfortable and present with clinical problems associated with weight gain [5]. Therefore, abnormal eating behaviours may lead to considerable morbidity in a significant proportion of AD patients. However, very little is known about the pathogenic mechanisms underlying eating changes in AD. In considering the possible neurochemical substrates of these behaviours, converging data from animal studies and clinical observations point to a critical role of the central serotonergic system in regulating normal and abnormal eating behaviours as well as related functions like satiety [9–11]. For example, selective serotonin reuptake inhibitors (SSRIs) have shown efficacy in the treatment of bulimia nervosa and binge eating disorders [12–14], as well as suppressing rebound hyperphagia in rats [15]. Furthermore, serotonin 5-HT 1A and 5-HT 4 receptors have been implicated in the regulation of feeding behaviour [16–19]. Additionally, positron emission tomography studies using receptor-specific radioligands have found persistent alterations of neocortical 5-HT 1A and 5-HT 2A receptors in patients recovering from bulimic eating disorders [20–22]. Interestingly, 5-HT receptor deficits are also found in the neocortex of frontotemporal dementia, which is characterized by neurobehavioural disturbances including carbohydrate craving and hyperorality [23,24]. Finally, we and others have shown perturbations of various serotonergic markers in the AD neocortex, some of which correlated with cognitive decline and a diverse range of neuropsychiatric behaviours [25–33]. Taken together, these data suggest that perturbations of neocortical serotonergic markers may underlie hyperphagic eating behaviours in AD.

In this study, we measured 5-HT 1A, 5-HT 2A, 5-HT 4 receptors as well as serotonin reuptake sites (also known as serotonin transporters, 5-HTT) in the postmortem neocortex of a cohort of AD patients who had been prospectively assessed for eating changes and other neuropsychiatric behaviours. We then correlated the presence of hyperphagic eating changes with the neurochemical measurements.

2. Materials and methods

2.1. Radioligands and other chemicals

[3H]Hydroxy-N,N-dipropyl-2-aminotetralin (8-OH-DPAT, specific activity 140–142 Ci/nmol, binds 5-HT 1A receptors) and [3H]ketanserin

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