Serotonin response in sweet-food craving Alzheimer’s disease subjects

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ABSTRACT. Abnormal sweet-food craving may occur in subjects with Alzheimer’s disease. This behavior may be due to abnormalities in the brain serotonin system. Fenfluramine stimulates the brain serotonin neuro system, producing an increase in systemic prolactin. Using the fenfluramine stimulation test, brain serotonin system response was evaluated in 12 subjects with probable Alzheimer’s disease. The subjects’ caregivers completed questionnaires concerning subject food preferences and behaviors. Alzheimer’s disease subjects with sweet-food craving were found to have a significantly higher response to fenfluramine than non sweet-food craving subjects. This preliminary study is limited by small sample size. Allowing for assumptions concerning central nervous system regulatory processes, the data suggest a possible role for the serotonin system in sweet-food craving in Alzheimer’s disease.

INTRODUCTION

Memory loss is universal in patients with Alzheimer’s disease (AD). However, for caregivers, often it is not memory loss but abnormal behavior that causes the most stress and leads ultimately to nursing home placement (1). Behaviors range from inconveniences to disruptive or threatening behaviors (2). Why these behaviors occur in some patients but not others is unknown. Abnormal behaviors are not easily attributable to memory loss, but may be due to other pathologic changes (3).

Memory loss in AD is thought to be due to loss of neurons in the brain acetylcholine system (4). However, neurons in other systems such as the serotonin (5 hydroxytryptophan, 5HT) system may also be involved. There may be a reduction of 60% in serotonin binding sites in the temporal lobe of AD patients (5, 6). Serotonin system abnormalities in AD may be separate from acetylcholine system loss (7). Abnormal behaviors may be related to brain serotonin system abnormalities (8, 9).

An abnormal behavior that has been associated with AD is sweet-food craving (10). An association between food preference and the serotonin system in normal subjects has been postulated for some time. There is some evidence to suggest that serotonin deficiency is associated with carbohydrate craving and compulsive eating disorders (11, 12).

It is postulated that serotonin deficiency causes dysphoria, and that food, especially carbohydrates (13), replenishes brain serotonin by increasing the serotonin precursor, tryptophan, thereby relieving the dysphoria. Serotonin deficiency would create a “drive” for carbohydrate food. Increased serotonin has a negative feedback effect to suppress appetite (14, 15).

AD subjects with serotonin deficiency may, under this hypothesis, have increased drive for carbohydrates, manifested as sweet-food craving.
Previously, there has been no clinically applicable way to assess central serotonin system activity. Recently, however, several challenge tests have been developed that show promise as useful estimators. When activated, the serotonin system stimulates the pituitary to produce prolactin, a hormone readily measured in peripheral blood. Fenfluramine, an FDA approved drug used in weight control as an appetite suppressant, is known to stimulate the serotonergic system, and hence produces an increase in systemic blood prolactin level (16). The fenfluramine stimulation test has been used to evaluate the brain serotonin axis in depression and personality disorders (17). Age and gender effects on the fenfluramine challenge test have recently been published (18).

In general, chronic low levels of a neurohormone cause increased sensitivity or upregulation of receptors for the neurohormone. For example, depletion of the serotonin system by the toxin tetrobenazine causes an upregulation or increased number of 5 HT (serotonin) receptors (19, 20). In cases of relative 5HT deficiency, receptor upregulation may cause an exaggerated prolactin response, which could be measured in peripheral blood. Thus, the fenfluramine challenge test may offer a clinically convenient way to identify AD patients with alterations in central serotonin activity.

This study explores the association between abnormal behaviors and central serotonin system activity in subjects with probable Alzheimer’s disease. Specifically, it tests associations between certain behaviors and a serotonin challenge test. It is hypothesized that AD subjects with abnormal behaviors are more likely to have decreased serotonin activity.

**METHODS**

We completed a fenfluramine challenge test in twelve subjects with probable Alzheimer’s disease using NINCDS/ADRDA criteria (21). Subjects were evaluated using a medical history and physical examination, blood tests for thyroid, vitamin, and other biochemical abnormalities, and neuroimaging (head CT or MRI); none was taking psychoactive medications, nor did medical records indicate such medications had been taken in the past month. Psychoactive medications were defined as any mood altering or centrally acting drug, including centrally acting antihypertensives.

After consent was obtained, subjects came to the Geriatrics Clinic fasting. Appointments were scheduled for 8:30 a.m. A baseline blood prolactin (PRL) sample was drawn, and subjects were given oral fenfluramine at a dose of 1 mg/kg. A second blood PRL sample was obtained 1.5 hours later. Baseline prolactin (PRL-1) and 90-minute prolactin (PRL-2) samples were analyzed by the hospital Clinical Lab. Caretakers completed questionnaires concerning the subject’s eating behavior (10). “Sweet-food craving” was tested with the written question, “Has he/she developed a preference or craving or strong desire for any particular kinds of food since the symptoms of dementia began?” The characteristic was defined as being present if the caregiver responded to this open-ended question by filling in “sweet foods” or some variant of that response (10). Additionally, caretakers completed a yes/no version of the BEHAVE-AD questionnaire, which lists 25 abnormal behaviors (22). “Psychotic symptoms” were defined as present if the caregiver answered “yes” to any problem area related to paranoia, misidentification, hallucinations or delusions. Similarly, “agitation” and “sleep disturbance” were defined from BEHAVE-AD responses. Folstein Mini-Mental Status Exam (MMSE) scores were also obtained for the subjects (23).

In this sample of probable Alzheimer’s disease subjects, the average age was 76 (SD = 8.2) years, and the mean MMSE score was 12.7 (SD = 7.8). Eight of the 12 subjects were female. No subjects were known to have diabetes or thyroid disorders.

**RESULTS**

All subjects had an increase in PRL after fenfluramine stimulation. The mean post-stimulation blood level at 90 minutes (PRL-2) was 10.43 ng/mL (SD = 4.7)

Subjects were divided into two groups: those whose PRL-2 levels were above the mean, and those whose levels were below the mean. Groups were compared by characteristics identified by