Brain metabolic and clinical effects of rivastigmine in Alzheimer’s disease

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Abstract

In-vivo metabolic measures with positron emission tomography using 18F-fluorodeoxyglucose (FDG-PET) have demonstrated hypometabolism in temporal, frontal, and hippocampal areas during the early stages of Alzheimer’s disease (AD). Progression of the dementia in AD involves compromised cholinergic functioning. Cholinesterase inhibitors have demonstrated efficacy in improving cognition and behaviour in AD. In this study, we demonstrate the usefulness of FDG-PET in measuring the progression of untreated AD and its modification by treatment with rivastigmine (Exelon, Novartis Pharmaceuticals, East Hanover, New Jersey, USA), a centrally selective cholinesterase inhibitor of the carbamate type. Patients with mild to moderate probable AD (Mini-Mental Status Exam scores of 10–26, inclusive) were enrolled in a double-blind, placebo controlled comparison of three fixed daily doses of rivastigmine (3, 6, or 9 mg/d) or placebo for 26 wk. FDG-PET scans were obtained on 27 patients at baseline and following 26 wk of treatment using the Snodgrass Picture Naming activation task. A total of 71.4% of the patients treated with placebo deteriorated clinically compared to only 25.0% of the patients treated with rivastigmine ($p^2 = 4.8; p < 0.03$). Rivastigmine-responders (i.e. those who clinically improved or remained clinically stable as measured by the Clinician’s Interview-Based Impression of Change-plus) showed a marked increase in brain metabolism ($p < 0.01$) involving, but not limited to, structures comprising the memory-related cortices and the prefrontal system. These metabolic changes were not observed in the placebo-treated patients or the rivastigmine non-responders. Of note is that responders increased hippocampal metabolism by 32.5% ($p < 0.03$) compared to a non-significant decrease in the non-responders (6.4%) and placebo-treated patients (4.1%). These results are consistent with the literature suggesting that FDG-PET can sensitively measure the progression of AD and its improvement with cholinesterase inhibitors. Rivastigmine prevented the expected deterioration in clinical status and dramatically increased brain metabolic activity in a majority of patients.

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Introduction

Most types of dementia show significant changes in brain glucose metabolism. Positron emission tomography (PET), which measures regional cerebral blood flow and/or metabolism, has been suggested to have the capability to detect functional abnormalities before structural changes appear in the degenerative dementias (Ichimiya, 1998). In studies of Alzheimer’s disease (AD), PET scanning demonstrated that patients with AD (mean age 69.1 yr) had significantly lower local cerebral metabolic rates for glucose (LCMR-gl) than 11 age-matched neurologically normal volunteers (mean age 66.3 yr) (McGeer et al., 1986). In fact, in patients with AD, values for cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO2), and cerebral metabolic rate for glucose (CMR-gl) have been shown to drop by 30–50% in comparison to age-matched normal controls (Kitamura and Terashi, 1990). The severity of the decline in LCMR-gl parallels the severity of the dementia and correlates with regional cortical neuronal loss and glial proliferation (McGeer et al., 1986).

AD is distinguished from other dementia syndromes by a characteristic pattern of decreased glucose metabolism, most prominent in temporal, prefrontal and parietal...
association cortices, with sparing of the primary sensory and motor cortical areas, basal ganglia, thalamus, brainstem, and cerebellum (Heiss et al., 1991; Mielle and Heiss, 1998; Small and Leiter, 1998). A similar pattern of metabolic disturbance was noted earlier by Szélies et al. (1986) who found a significant reduction in total cortical glucose metabolism most marked in the parietal and the adjacent regions of the temporal and occipital association cortices. Other regions, however, were largely spared from the reduction in metabolism (e.g. primary somatosensory and visual cortex) or even showed slightly enhanced metabolic rates (e.g. cerebellum).

The brain regions most affected by the disease change over time. During clinical stage I AD, reductions in CBF and CMR-O2 are prominent in the temporal and the parietotemporal transition cortices which reflect the initial and hallmark memory deficits. In clinical stage II, reduction in the parietal cortex also becomes quite marked, and in clinical stage III the prefrontal cortex is implicated as well (Kitamura and Terashi, 1990).

PET has demonstrated three alterations in AD that are related to functional deficits. First, whole-brain metabolic rate is reduced. These reductions are proportional to overall severity of dementia. Secondly, regional metabolic rates in the association cortices demonstrate greater reductions than are observed in the primary sensory and motor cortices, corresponding to marked impairment of higher cognitive function and relative sparing of sensory and motor function. Thirdly, regional metabolic rates in the association cortices demonstrate increased hemispheric asymmetry relative to controls (Haxby and Rapoport, 1986). Rapoport (1997) has suggested that these metabolic alterations can be used to convert a ‘possible’ to a ‘probable’ diagnosis of AD by the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria. FDG-PET has been suggested to be useful in routine clinical evaluation of AD (Frey et al., 1998; Perani, 1999; Small and Leiter, 1998). Thus, FDG-PET may play an important role in establishing the diagnosis. Nagata et al. (2000) report that O-15 PET ligands can aid in distinguishing vascular dementia from AD. Other PET radiotracers have been used to aid in the diagnosis of AD (Kuhl et al., 1999).

The therapeutic effects of medications have been demonstrated with PET. For example, before and after 6 months of treatment, 40 patients with ‘probable’ AD underwent FDG-PET scans. Treatment consisted of either cognitive training or cognitive training plus phosphatidylserine. Prior to treatment, groups were not different in their regional cerebral metabolic rates. Patients who received a combination of cognitive training and phosphatidylserine as treatment showed a significant glucose enhancement, which was greatest during the PET activation tasks, compared to those who received only cognitive training (Heiss et al., 1991, 1993).

PET studies indicate that long-term treatment with tacrine, a non-competitive inhibitor of acetylcholinesterase, in AD patients with mild dementia improves functional activities in the brain (Nordberg, 1993). Changes in glucose metabolism and improvement in nicotinic receptor function were observed after 3 months of treatment. The most significant effects were found in patients with early forms of the dementia (Nordberg, 1993, Nordberg et al., 1997).

As a final example, patients treated with the acetylcholine releaser linopirdine showed an increase in regional cerebral blood flow (rCBF) in parietal cortex of 4.1 ± 5.8% whereas those treated with placebo showed a decrease of −2.0 ± 7.4% (p = 0.03) (van Dyck et al., 1997). Together, these data support the conclusion that rCBF and LCMR-gl abnormalities in AD are functionally related to the disease and can be selectively altered with pharmacological interventions. Thus, we hypothesize that patients successfully treated with rivastigmine, a centrally selective cholinesterase (acetyl- and butyryl-) inhibitor, will demonstrate a different brain metabolic pattern from those patients who do not respond to rivastigmine or are treated with placebo.

Methods

Sample

Our centre was one of 15 participating in a multicentre, placebo-controlled trial investigating the effects of rivastigmine in probable AD. The PET scanning procedure, in which 27 patients participated, was conducted at our site only. Eligible patients were aged between 45 and 89 yr (of non-childbearing potential) who fulfilled the criteria for dementia of the Alzheimer’s type described in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994), who had probable AD according to the criteria of the NINCDS-ADRDA (McKhann et al., 1984), and whose impairment was mild to moderately severe based on a MMSE score between 10 and 26 (both inclusive). Each patient had a responsible caregiver and, along with their caregiver, provided written, informed consent. Most patients with concomitant diseases were included; only those with severe and unstable medical illnesses were excluded. Patients were allowed to continue most medications for coexistent diseases; however, anticholinergic drugs, acetylcholine precursor health food supplements, memory enhancers, insulin, and psychotropic drugs were not permitted other than the occasional use of chloral hydrate (500 mg/d) for agitation or insomnia. The
procedures followed were in accord with the Ethical Standards of the Institutional Committees on Human Experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

**Study design**

Twenty patients were treated with rivastigmine (Exelon, Novartis Pharmaceuticals, East Hanover, New Jersey, USA) and 7 with placebo in a double-blind, random assignment design for 26 wk. Patients in the treatment group were randomized to 1 of 3 fixed doses of rivastigmine (3, 6, or 9 mg/d). Patients were titrated to their assigned dose over a 12-wk period and then followed-up for a 14-wk fixed-dose phase.

An experienced clinician, who was blind to drug assignment, interviewed the patients and their caregivers separately to ascertain sufficient information to complete the Clinician’s Interview-Based Impression of Change Plus (CIBIC-plus). The CIBIC-plus is a semi-structured interview, which systematically assesses short- and long-term memory, orientation, judgement and problem solving, and praxis and verbal fluency. The CIBIC-plus is scored by a single global rating summarizing all domains on a 1- to 7-point scale, with a score of 4 indicating no change from baseline. Scores of 1–3 indicate patients’ improvement relative to baseline. Scores of 5–7 indicate patients’ deterioration relative to baseline. AD is a progressive illness with expected declines in the CIBIC-plus over a 6-month period. Patients who scored 1 ('markedly improved') to 4 ('unchanged') evidenced no progression of the illness and were called ‘rivastigmine-responders’. Patients who scored 5 ('minimally worse') to 7 ('markedly worse') had clinically deteriorated and were called ‘rivastigmine non-responders’.

**FDG-PET**

FDG-PET scans were obtained on the 27 patients at baseline and following 26 wk of treatment during a picture-naming activation task (Snodgrass and Vanderwart, 1980). The picture-naming task was administered by computer for the entire 32 min of FDG uptake. The FDG dose was approx. 5 mCi. Patients were PET scanned at the University of California, Irvine Brain Imaging Center using a GE 2048 dedicated head scanner. Thirty slices at 6.5-mm intervals (15 in each of two sets) were obtained so as to cover the entire brain. Scans were reconstructed with a blank and a transmission scan. A thermostetting plastic facemask was used to hold the subject stationary during the 60 min of total image acquisition. The transmission scan was used as an attenuation correction for scan reconstruction. The rate of glucose metabolism was calculated on a 3-constant model using arterialized blood samples from the warmed arm following the validation studies of Phelps et al. (1979).

**Statistical analyses: general**

For contrasting baseline characteristics and continuous clinical changes, 2-tailed Student’s *t* tests or ANOVAs were performed. For categorical analysis, *χ*² tests were calculated.

**Statistical analyses: PET scans**

Each subject’s PET data were transformed into a standard brain space so that pixel-by-pixel comparisons could be made between each subject’s before and after treatment scans. These differences were then compared following methods based on those of Friston et al. (1991). Results were displayed on a standardized MRI based on the Matsui and Hirano (1978) stereotaxic brain atlas (Figure 1). Pixels with statistically significant *t* test differences at *p* levels < 0.03, following a Monte Carlo thresholding as described below, were displayed. Anatomical localization was accomplished through the concordance of Talairach and Tournoux coordinates (1988), an in-house probabilistic brain atlas, and confirmation by a neuroanatomist (J.F.) who was blind to group assignment. The Talairach and Tournoux coordinates are provided in parentheses following the relevant brain regions.

A resampling based image cluster analysis (discussed in greater detail in Wu et al., 1997) was used to estimate the probability for a given profile of contiguous connected clusters exceeding the probabilistic threshold of *p* < 0.03. The probabilities of a given size contiguous cluster were assessed using this distribution. Monte Carlo simulations using sample sizes corresponding to the *ns* in our comparisons were run using our normal control pool with 100 random drawings to empirically determine the distribution (Good, 1994; Pollack et al., 1994; Sobol, 1975; Widman, 1988). The Monte Carlo simulation with a 0.03 significance level protected against Type I errors due to multiple comparisons. The *p* map calculated from the actual experiment was then analysed with a threshold that had been corrected for randomly significant *t* tests (Figure 1). All significant pixel clusters whose sizes were less than the threshold cluster size were thus eliminated.

**MRI template**

Magnetic resonance imaging (MRI) data were available for 12 rivastigmine-responders, 4 rivastigmine non-responders, and 3 placebo-treated patients. MRI templates from the baseline scan were used to outline the hippocampus proper and co-register with the PET data using
the AIR 3.08 module of MEDx (Woods et al., 1998). At 6 months, a second MRI for co-registration was not obtained. Therefore, the baseline MRI was used for outlining the 6-month PET scan. However, because de Leon (1997) has shown hippocampal shrinkage over this period of time, the analysis was confined to the central part of the hippocampal area (hippocampus and para-hippocampal gyrus at the MHS 9 level), as it was the area least likely to change. The MRI template was used as a confirmatory analysis for the hippocampal differences found for the entire sample.

**Results**

Twenty-seven patients (mean age, 75.9 ± 6.9 yr; range, 64–89 yr) participated in this study: 7 were treated with placebo, 5 with 3 mg/d rivastigmine, 7 with 6 mg/d rivastigmine, and 8 with 9 mg/d rivastigmine. The mean baseline MMSE of the patients who were PET scanned was 20.4 with a range of 15–26, implying that the patients had mild-to-moderate dementia. Of those patients receiving rivastigmine, 15 clinically responded whereas 5 did not, based on the patients’ CIBIC-plus scores. Of the placebo-treated patients 71.4% deteriorated (CIBIC-plus scores of 5–7) compared to 25.0% of the rivastigmine-treated patients (χ² = 4.8; p < 0.03) (Table 1).

On entrance to the study, there were no statistically significant differences in age, MMSE scores or Global Deterioration Scores between the placebo-treated, rivastigmine-responder, and rivastigmine non-responder groups. No statistical differences in mean doses of rivastigmine between the rivastigmine responders and non-responders were observed.
Table 1. Global CIBIC-plus scores in PET scanned patients

<table>
<thead>
<tr>
<th>Score</th>
<th>Placebo</th>
<th>Rivastigmine</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilized (1–4)</td>
<td>2</td>
<td>15</td>
<td>4 (unchanged), 3 (minimally improved), 2 (moderately improved), 1 (markedly improved)</td>
</tr>
<tr>
<td>Deterioration (5–7)</td>
<td>5</td>
<td>5</td>
<td>5 (minimally worse), 6 (moderately worse), 7 (markedly worse)</td>
</tr>
</tbody>
</table>

χ² = 4.8; p < 0.03.

The main PET finding was a significant 26.5% increase in global CMR-gl in the rivastigmine-responders (p < 0.01) compared to a non-significant 6.2% increase in the non-responders (p = 0.06) and a non-significant 8.6% increase in the placebo-treated patients (p = 0.5). Significant regional metabolic differences were observed for the placebo-treated patients (Figure 1). Specifically, for the placebo-treated patients, metabolic increases in the orbital cortex, the occipital pole of the visual cortex, medial thalamus, and mesopontine tegmentum were observed. The non-responders very much resembled the untreated patients with the exception of a slight increase in midbrain metabolism.

For the rivastigmine-responders, marked metabolic increases were found in memory-related cortices [dorsolateral prefrontal cortex (±41, +36, 10), parahippocampal gyrus]. Secondarily, there were some significant increases in the ‘prefrontal system’: the orbital cortex, medial thalamus (+5, −19, +10; overlapping the mediodorsal and midline areas), mesopontine tegmentum [overlapping the substantia nigra-ventral tegmental area (±15, −21, −4) and retrorubral field, amygdala (+18, −5, −16), and substantia inominata (±12, 0, −5; which includes the ventral striatum (±15, 7, 0)/pallidum, extended amygdala and cholinergic/GABAergic nucleus basalis). The least amount of metabolic increase was observed in the primary and secondary sensory cortices [e.g. visual cortex (−5, −95, +10)].

There were no statistically significant differences between the placebo-treated patients and the rivastigmine-treated patients at baseline.

A region of a priori interest was the hippocampus. The metabolism of the hippocampal area (hippocampus and parahippocampal gyrus at the MHS 9 level) bilaterally was determined for each PET scan. After 6 months of treatment, a mean 32.5% absolute metabolic increase was observed in the rivastigmine responders (p < 0.03) in contrast to an absolute metabolic decrease of 6.4% in the rivastigmine non-responders (ns) and 4.1% decrease in the placebo-treated patients (ns) (see Figure 2). In a confirmatory analysis available for a subset of patients, the MRI template obtained at baseline was co-registered to the baseline and after treatment PET scans. A significant increase (p < 0.05) was found for the rivastigmine responders in contrast to no significant change for the rivastigmine non-responders and placebo-treated patients.

The primary visual cortex (Brodmann area 17), receiving less dense cholinergic innervation, showed no significant change in absolute glucose metabolism in any of the three groups after 6 months of treatment (t = 0.75, t = 0.35; t = 1.39, respectively) or between groups [F (2,24) = 0.57; p = 0.6].

There was no whole-brain metabolic dose–response curve for oral rivastigmine (F = 0.62, p = 0.55). Performance on the Snodgrass Picture Naming activation...
task (i.e. number of correct responses) was not statistically significant between groups or across time.

**Discussion**

AD patients who have benefited from rivastigmine treatment demonstrated different brain glucose metabolic patterns than those patients who did not benefit from rivastigmine, or who were treated with placebo. The rivastigmine non-responders showed no significant changes in absolute CMR-gl whereas rivastigmine-responders showed a marked metabolic increase, including areas of memory-related cortices and the prefrontal system.

Differential effects were also observed regionally. Specifically, in the placebo-treated patients, the sensory cortices increased in metabolism as did the thalamus, mesopontine tegmentum, and the ventral prefrontal cortices. This pattern may reflect the degeneration of higher-order sensory and anterior association cortices, which is commonly observed with the progression of untreated AD. This degeneration could be associated with a lack of high-order feedback to the primary sensory cortical areas and, therefore, compensatory gain, which could be reflected by an increase in sensory cortical metabolism, as seen in the present study. A similar pattern of decreased frontal-posterior functional interconnections, with disruption of feedback to the visual cortices, was observed by Horwitz et al. (1995). Successful treatment with rivastigmine clearly altered this pattern. In particular, the regional metabolic increases in the visual cortex did not occur.

The changes observed in the prefrontal system – orbital cortex, medial thalamus, mesopontine tegmentum, substantia nigra-ventral tegmentum area, amygdala and substantia inominata (which includes the ventral striatum/pallidum, extended amygdala and cholinergic/GABAergic nucleus basalis) – in the rivastigmine-responders may be related to dopamine as well as the expected effects on acetylcholine. The consistent differential changes observed in the prefrontal system between rivastigmine-responders and placebo-treated patients are of note. The prefrontal system is involved in both procedural and emotional memory functions as well as limbic and cognitive tasks. Deficits in appropriately responding to emergencies and interpersonal social conflicts are commonly observed in the moderately severe AD patient. Emotional memory itself, however, has not been well studied in AD although our unpublished data are consistent with deficits in both emotional and non-emotional memory in AD patients.

Weinstock (1999) reviews animal and human data that show increasing the cholinergic transmission in the basal forebrain and hippocampus increases brain glucose metabolism and reduces the associated memory deficits. Our data suggest that when cholinesterase inhibitors are not able to increase glucose utilization, as in our rivastigmine non-responders, the cognitive deficits associated with AD are not attenuated. Non-response to medication is an acknowledged aspect of all clinical trials. This study offers brain metabolic data relevant to failure to respond to cholinesterase inhibitors. The reasons why some AD patients do not increase their metabolism following cholinesterase inhibitors is not known and requires further investigation.

A number of caveats are in line regarding our findings. First, the patient cohorts used were relatively small. Although there was no dose response in whole-brain metabolism (ns) in this study, a full dose–response analysis could not be conducted. This may be significant, as clinical response to rivastigmine appears to be dose-related. Also, patients were followed for 6 months, which is a relatively short period of time given the average duration for AD of 8 yr. With a longer follow-up the placebo-treated group would be expected to show more areas of progressive decrease in metabolism. Nevertheless, we did observe a numerical metabolic decrease of 4.1% in the hippocampus of the placebo-treated group. This non-significant hippocampal metabolic decrease in the placebo-treated patients as well as in the rivastigmine non-responders was not due to a global difference in brain metabolism as there were non-significant whole-brain increases in metabolism for both groups. It is striking that the non-responders and untreated patients failed to increase their hippocampal metabolism in spite of an overall increase in whole-brain metabolism. This is in striking contrast to the 32.5% increase in hippocampal metabolism in the rivastigmine-responders in the context of a 26.6% increase in whole-brain metabolism. The use of PET to document the effects of treatment has some advantages over traditional outcome measures. First, in this study we were able to document treatment effects using a relatively small number of subjects whereas traditional clinical trials require several hundred subjects to effectively demonstrate treatment effects. Even larger clinical trials are required to demonstrate delay in the progression of AD. Moreover, PET evaluations may be more objective than typical, qualitative measures such as the CIBIC-plus and Alzheimer’s Disease Assessment Scale (ADAS). The results from such traditional clinical measures are often confounded by problems in reliability and sensitivity, fluctuating subject attention, and further constrained by caregiver capacities, important in accurately completing rating scales such as the CIBIC-plus. PET overcomes some of these limitations by providing a quantitative measure of cerebral metabolism.
The significant metabolic findings in this study may be due in part to the sensitivity of the activation task used. Changes in hippocampal metabolism are not typically found in SPECT and PET investigations when patients are studied in the absence of an activation task (i.e., at rest). A recent study by Pietrini et al. (1999) demonstrated that activation PET is a more sensitive index of the functional/metabolic failure of neuronal systems in AD than PET metabolism at rest. We utilized a task (the Snodgrass Picture Naming activation task) that is sensitive to a cognitive domain (object naming) performance, which is impaired in AD. Further, this task does not suffer from floor or ceiling effects, unlike most memory tasks. Therefore, motivation, apathy, and discouragement were controlled for during the task. The Snodgrass activation task was used for all scans. There were no significant differences in Snodgrass performance between groups across the 6 months of the study. Thus, the metabolic differences observed between the groups were not a function of performance on the activation task.

Future studies utilizing larger groups with a range of patients across disease phases are clearly warranted. Moreover, these investigations should include an analysis correlating clinical neuropsychological factors and dose with the observed changes in neural circuits. Nevertheless, the data presented indicate that, even without such extensions, FDG-PET has the ability to reflect the natural progression of AD, to reflect clinical improvement; and to distinguish drug effects from treatment response. In this clinical sample, rivastigmine prevented the clinical progression in the symptoms of AD over a 6-month period and increased activation of global brain metabolism, including relevant memory-related and prefrontal circuits systems during a cognitive task in those subjects responding to rivastigmine.

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References


