A Double FDG/PET Study of the Effects of Scopolamine in Older Adults

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Two consecutive positron emission scans were done in one session using a double injection method of [^{18}F]2-fluoro-2-deoxyglucose administration to examine the effects of the antimuscarinic drug scopolamine on cerebral glucose metabolism in ten older adults. Scopolamine causes temporary memory impairment, and its effects have been used to model aspects of the cognitive impairment that occur in Alzheimer's disease (AD). Cortical metabolic rates of patients with AD have been reported to be depressed, especially in parietal, temporal, and frontal association areas. After scopolamine

administration to the elderly volunteers, absolute and normalized glucose metabolic rates were depressed in prefrontal and occipital regions and increased in parietal-occipital cortical regions and a left middle temporal region. These changes in the older volunteers are generally not consistent with changes seen in AD. We conclude that deficits in muscarinic system function may contribute to some but not all of the hypometabolic changes seen in AD patients.

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The anticholinergic drug scopolamine causes temporary memory impairment and has been used to explore the role of the muscarinic cholinergic system in memory processes in both animals and humans (Drachman and Leavitt 1974; Bartus et al. 1982; Kopelman and Corn 1988; Molchan et al. 1992). It has been used to model

aspects of the memory impairment that occurs in normal aging (Drachman and Leavitt 1974; Molchan et al. 1992) and Alzheimer's disease (AD) (Sunderland et al. 1986; Molchan et al. 1992, for review). The pathological changes in the muscarinic cholinergic system of patients with AD are thought to contribute to the severe memory impairment that occurs in this disease (Davies and Maloney 1976; Perry et al. 1978; Bartus et al. 1982; Whitehouse et al. 1982). Patients with AD have been shown to have decreased cerebral blood flow (CBF) and metabolic rates in the cerebral cortex, with the greatest reductions in parietotemporal regions, and with more frontal involvement later in the disease process (Frackowiak et al. 1981; Foster et al. 1983; Haxby et al. 1988; Friedland et al. 1989; Kumar et al. 1991). It is unknown what neuropathological changes in the brain relate to the decreases in metabolic rate. In this study, using (^{18}F) 2-fluoro-2-deoxy-D-glucose (FDG) in a double injection paradigm, we sought to explore whether metabolic rate patterns after acute scopolamine administration in older adults were analogous to patterns seen in unmedicated AD patients.

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Many studies have utilized positron emission tomography (PET) to explore the effects of psychoactive medications in various patient and normal control groups (Sedvall et al. 1986; Honer et al. 1988; Frey et al. 1992; Gitelman and Prohovnik 1992). Most prior PET studies though, in looking at effects before and after medication, have done so on different days. This is necessary for examining drugs such as tricyclic antidepressants, which may take weeks to induce their therapeutic effects. When studying the acute effects of a drug, scanning subjects before and after drug administration in the same session is likely to improve sensitivity. This is because variability is decreased when the subject does not have to be repositioned in the scanner (Phelps et al. 1984; Bartlett et al. 1988), when possible state changes across a long span of time are avoided, and when each subject serves as his or her own control (Phelps et al. 1984). In this study, we used a double injection paradigm (Brooks et al. 1987; Chang et al. 1987) using (^{18}F) 2-fluoro-2-deoxy-D-glucose (FDG) to explore the acute metabolic effects of scopolamine in a group of older normal volunteers.

METHODS

This study was approved by the Internal Review Board of the National Institute of Mental Health and the Radiation Safety Committee of the National Institutes of Health. Informed consent was obtained from all subjects.

Subjects

Ten older normal volunteers (Table 1) participated in the study after informed consent and screening to exclude medical and psychiatric illness and family history of dementia or other neuropsychiatric disease. Their evaluation consisted of physical and mental status examinations, electrocardiogram, MRI scan of the brain, and laboratory tests for hematologic, hepatic, renal, and thyroid function. They also completed a battery of neuropsychological tests, which included the Wechsler Memory Scale-Revised (WMS-R) (Wechsler 1987), to ensure normal memory and other cognitive function. They were paid for their participation and were drug-free for at least three weeks prior to the study.

Table 1. Demographic Data on Ten Normal Volunteers

	Mean $\pm$ SD
Age (years)	62.8 $\pm$ 8.8
Education (years)	17.6 $\pm$ 2.6
Wechsler Memory Scale	125.7 $\pm$ 10.8
Weight (kg)	69.4 $\pm$ 15.0
Gender: 5F, 5M	

PET Scan Procedure

Subjects were fasting, and remained supine with eyes and ears uncovered throughout the scans, including the transmission scan, which was used to calculate attenuation. The scanner (Scanditronix, Essex, MA) has a full-width half-maximum in plane resolution of 5 to 6 mm and a z-axis resolution of 11.8 mm. Blood samples from the radial artery were obtained to calculate the tracer input curve. Subjects were free to open and close their eyes; the room was quiet, and no cognitive tasks were done. Each was fitted with a plastic hexalite face mask, which was fixed to the scanner headrest.

The first FDG injection (3.0 millicuries or 111 MBq) was administered at time 0 through an indwelling intravenous line; this was followed by a 30 minute uptake period. Emission scanning then commenced for 30 minutes. After completion of the first emission scan, 0.5 mg of scopolamine hydrobromide was given intravenously over one minute. Thirty minutes later (within the 110 minute half-life of the first injection), the second FDG injection (5 millicuries or 185 MBq) was administered. As for the first scan, emission scanning followed a 30 minute uptake period (Figure 1). The residual radioactivity from the first injection was measured and subtracted from the counts measured during the second scan. The method used for this correction is based on an estimate of k_4 , which is the dephosphorylation rate of FDG and the rate of decay of ^{18}F (Brooks et al. 1987).

The dose of scopolamine was chosen based on a prior study of a range of doses which showed that a statistically significant decline in cognitive test performance in older volunteers occurred at the 0.5 mg dose (Sunderland et al. 1986; Molchan et al. 1992). In the authors' experience, all subjects administered this dose experience cognitive impairment. The timing of the scans was based on prior studies showing that the amnesic effects of IV scopolamine occur to a consistent degree 60 to 150 minutes after administration (Sunderland et al. 1987; Kopelman and Corn 1988; Molchan et al. 1992).

Twenty-one slices were acquired during each of the two scans, starting at 5 mm above the plane parallel to the canthomeatal (CM) line. The interslice interval was approximately 3.5 mm.

Regions of Interest Analysis

Sixty regions of interest (ROI) were measured in five standard transaxial planes (Figure 2) (plane A, 94 mm above the CM line; plane B, 81 mm above the CM line; plane C, 67 mm above the CM line; plane D, 53 mm above the CM line; and plane E, 40 mm above the CM line) by a staff member experienced in the technique and blind to subject identity and drug condition. Since

Figure 1. Study design.

the double FDG procedure eliminates repositioning the head for each scan, the five planes selected in the first scan were matched exactly to the same slices or images in the second scan. ROIs were primarily from cortical areas, although ROIs which included the thalamus (D plane), basal ganglia (D plane), hippocampus (E plane), and cingulate gyrus (B plane) were also sampled.

ROIs, which were 7 mm × 7 mm boxes, were placed in a semi-automated procedure through neuroanatomical matching to a standard PET template based on the brain atlas of Matsui and Hirano (1978), as has been previously described (Clark et al. 1985; Cohen et al. 1988). Prior studies have shown that the interater reliability of this method of choosing ROIs is very high ($r > 0.95$) (Semple et al. 1993).

Raw pixel values were converted to glucose metabolic rates in milligrams of glucose per 100 g of tissue per minute (Brooks 1982). Metabolic rates are expressed as global glucose metabolic rates (estimates of the average value for glucose metabolism obtained from all the gray-matter-rich areas of the brain sampled), absolute regional glucose metabolic rates (average values

for glucose metabolism obtained from the region of interest), and normalized regional glucose metabolic rates (regional absolute metabolism rate/global metabolism rate). The normalization procedure was used to minimize the effects of individual variation in global metabolism on regional metabolism (Bartlett et al. 1988).

Statistics

Comparisons of global and regional metabolic rates between off- and on-drug scans were done using both absolute and normalized values. The analyses were performed using paired *t*-tests (two-tailed). In view of the exploratory purpose of the study and the small number of subjects, we chose to decrease the probability of Type II errors by omitting corrections for multiple comparisons. Although our hypotheses about metabolic changes after scopolamine could be limited to brain regions reported in previous PET studies, we felt that it would be more appropriate in our initial study in older adults to take advantage of the ability of PET to image large areas of the brain simultaneously.

Figure 2. Schematic representation of the regions of interest (ROIs) sampled in the left and right hemispheres. Regions labeled as medial, although sampled from the medial portion of the cortex, are represented when possible as incomplete boxes on the lateral surface of each hemisphere. Additional ROIs not pictured are left and right thalamus, caudate (head area), putamen (anterior and posterior regions), hippocampus, and the mid-cingulate region. Total number of ROIs is 60.

RESULTS

Global and Absolute Regional Cerebral Glucose Metabolism

Data are summarized in Figure 3. There was no significant change in global metabolic rate after scopolamine (7.41 ± 0.58 off-drug vs. 7.39 ± 0.95 mg glucose/100 g tissue/min on-drug). In six of the 60 ROIs a significant change in absolute regional glucose metabolism was detected. Decreased regional glucose metabolic rates were detected in three ROIs, two in prefrontal areas and one in occipital cortex. Increased metabolic rates occurred in left and right parietoccipital ROIs and a left middle temporal ROI.

Normalized Regional Cerebral Glucose Metabolism

Data are summarized in Figure 4. Changes were similar to the absolute data, with the exception of one of the prefrontal ROIs in which the change did not reach statistical significance.

Side Effects of Scopolamine

All subjects reported experiencing dry mouth after scopolamine administration. Six subjects experienced motor restlessness, manifested by leg movements; eight subjects were drowsy, and one was lightheaded. Side effects usually began within 15 minutes of injection and lasted throughout the procedure.

DISCUSSION

Using a double FDG/PET paradigm, we found that scopolamine significantly altered regional cerebral glucose metabolism in a number of brain areas in normal older volunteers. The decreased metabolic rates we observed in prefrontal cortex may relate to the inattentiveness and decreased ability to suppress inappropriate responses typical of AD (Fuld et al. 1982) and reported in normal subjects following scopolamine administration (Drachman and Leavitt 1974; Dunne and Hartley 1985; Broks et al. 1988). The decrease in metabolic rate after scopolamine in an area of the occipital cortex that includes primary visual cortex is consistent

Region	Off-drug	On-drug	<i>p</i>	% Change
A plane -				
ant. medial frontal	$9.30 \pm 0.98^*$	8.67 ± 1.53	0.04	-6.8
C plane -				
ant. medial frontal	8.99 ± 1.36	8.28 ± 1.67	0.05	-7.9
occipital	10.67 ± 1.37	9.65 ± 1.63	0.001	-9.6
left parietal/occipital	8.53 ± 1.11	9.16 ± 1.31	0.01	+7.4
right parietal/occipital	8.99 ± 0.95	9.71 ± 1.54	0.04	+8.0
D plane -				
left middle temporal	9.40 ± 1.03	9.99 ± 1.37	0.03	+6.3

Figure 3. Regions of the brain where glucose metabolism (absolute values) changed after scopolamine administration. The abbreviation ant. = anterior.

* means $\pm$ SD

with findings of others and with the presence of a fairly high concentration of muscarinic receptors in that region (Frey et al. 1992; Cohen et al. submitted). It is also consistent with scopolamine's effects on the visual evoked potential (Smith et al. 1990).

Increased metabolic rates after scopolamine in the left and right parietoccipital ROIs and a left middle temporal cortex ROI were unexpected. The parietoccipital ROIs are probably association areas, having to do with visual-spatial functions. The middle temporal lobe ROI probably includes auditory association cortex and primary auditory cortex. As one explanation, perhaps the increases are secondary to a disinhibitory mechanism on these areas, through other areas of the brain whose function was suppressed by scopolamine. Possibly, some areas with decreased metabolic rates may not be detected, especially in aged brains, in which CBF and metabolic rates have been reported to be already reduced in limbic and association cortices (Kuhl et al. 1982; Martin et al. 1991), although other studies indicate no alterations in these measures with age (Duara et al. 1984). If metabolic rates in aged brain are relatively reduced in these brain areas because of decreased numbers of neurons or any other reason, perhaps further

challenge with scopolamine may not produce a detectable change.

The most consistent abnormalities found with PET in AD patients are decreased metabolic rates in association cortices, especially parietotemporal (Frackowiak et al. 1981; Foster et al. 1984; Duara et al. 1986; Haxby et al. 1988), with frontal decreases more evident as the illness progresses (Frackowiak et al. 1981; Haxby et al. 1988; Friedland et al. 1989). Significant decreases in regional glucose metabolic rate in occipital cortex have also been reported (Foster et al. 1984; Friedland et al. 1989). Whether the blood flow/metabolic changes detected by PET are related to the muscarinic system deficit in AD patients is unknown. The decreased metabolic rates after scopolamine we found in prefrontal and occipital cortices are consistent with metabolic changes seen in AD brain, but the increased rates in parietoccipital and temporal lobe ROIs are not.

Three prior neuroimaging studies have examined the effects of scopolamine in humans. The first report used the ^{133}Xe inhalation technique in 15 young normal volunteers and found that global CBF, predominantly frontal lobe regional CBF, was reduced after scopolamine administration (Honer et al. 1988). Using

* means ± SD

Figure 4. Regions of the brain where glucose metabolism (normalized values) changed after scopolamine administration.

the same technique in seven elderly normal volunteers, Gitelman and Prohovnik (1992) found that after combined administration of scopolamine and the nicotinic antagonist mecamylamine, CBF was similarly reduced in frontal cortex. They also reported a decrease in parietotemporal cortex, similar to that found in AD, indicating that the combination of these two drugs replicated the CBF alterations reported in AD better than scopolamine alone. These findings are consistent with the known muscarinic (Bartus et al., 1982; Whitehouse et al., 1982) and nicotinic (Whitehouse et al., 1988) deficits in the illness. In another study, a group of young normal volunteers who had not received scopolamine were compared with a group who received 0.5 mg IV in a FDG/PET study. Decreased metabolic rates were noted in the thalamus, occipital, right frontoparietal, and cingulate cortices; increased metabolic rates were noted in the basal ganglia (Cohen et al. submitted). This study differed from the current one in a number of ways. Most notably, young normal volunteers were studied, and subjects performed a continuous performance task during the scans. Alterations in the cholinergic system have been reported to occur with age that may alter the response to scopolamine in aged subjects (Molchan et al. 1992). These age-related central cholinergic system changes include decreased acetylcholine synthesis and release (Decker 1987), as well as decreases in muscarinic receptor numbers (Nordberg and Winblad 1981; Rinne 1987).

In animal studies, scopolamine generally has been shown to decrease glucose metabolism in hippocampus and cortical areas, basal ganglia, and thalamus (Weinberger et al. 1979; Dam and London 1984; Helen and London 1984; Piercey et al. 1987; Ray et al. 1992), and cholinergic agonists, both muscarinic and nicotinic, to enhance glucose metabolism (Dam and London 1984; Harrell and Davis 1985; Soncrant et al. 1985; Hoffman et al. 1986; Churchill et al. 1987; London et al. 1988). Similarly, lesions of the nucleus basalis magnocellular (nbM) in animals, which is homologous to the nucleus basalis of Meynert in humans (the source of the cholinergic projection to cortex), results in decreased cerebral glucose metabolism, especially in frontal cortical regions (Lamarca and Fibiger 1984; London et al. 1984; Kiyosawa et al. 1989; Mihara 1989).

In one study of baboons given a left nbM lesion, cortical metabolic rate of glucose was suppressed in the ipsilateral cortex, with the greatest decrease in frontotemporal regions. These decreases correlated with decreases in choline acetyltransferase activity, indicating that cortical cholinergic differentiation had a role in the metabolic changes (Kiyosawa et al. 1989). It is not clear why some cortical regions, in this and prior studies, should have decreased metabolic rates relative to other cortical regions, as the distribution of muscarinic receptors throughout the cortex is relatively con-

sistent throughout the cortical lobes, with slightly higher binding in temporal cortex according to some studies (Lang and Henke 1983; Cortes et al. 1987). Perhaps receptor subtypes, which have different affinities for scopolamine, contribute to decreased metabolic rates in some areas but not others (Bonner et al. 1988). Using [^{11}C]scopolamine and PET to image muscarinic receptors in six young normal volunteers, Frey and colleagues found that the highest specific binding occurred in the basal ganglia and cerebral cortex (Frey et al. 1992), consistent with *in vitro* autoradiographic studies of human brain (Enna et al. 1977; Davies and Verth 1978; Lang and Henke 1983; Cortes et al. 1986; Lin et al. 1986; Cortes et al. 1987).

In summary, the alterations in regional glucose metabolic rates that we found in older volunteers using a double injection method of FDG administration with PET are consistent with some, but not all of the changes found in the brains of patients with AD. This may be due to the involvement in the disease of neurotransmitter systems besides the muscarinic cholinergic, which scopolamine targets, or to involvement of other pathological lesions such as amyloid plaques in areas of decreased metabolic rates (Honer et al. 1988). Also, five different muscarinic receptor subtypes have been identified using molecular biological techniques to date (Bonner et al. 1988). Future studies utilizing ligands specific to each subtype, when they become available, will enhance understanding of changes that occur in the aging brain and in dementia.

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