Assessment of Brain Cholinergic Function using Arterial Spin Labeling

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Introduction

The cholinergic system plays a key role in consciousness and attention processes (1-2). Cholinergic dysfunction occurs under a variety of conditions, including normal aging, dementia, and delirium (3). However, only a few studies have been reported using imaging to characterize the cholinergic system and underlying disease processes. Here we probe the cholinergic system by using pharmacological agents and then examining in vivo cerebral blood flow (CBF) changes caused by these drugs using the arterial spin labeling technique.

Methods

Fifteen young healthy subjects (age 21-35) participated in a randomized, placebo-controlled, double blinded crossover study. Cholinergic blockade was achieved using muscarinic blockade with scopolamine and nicotinic blockade with mecamylamine. Each subject underwent 4 pharmacologic conditions: 1) placebo; 2) mecamylamine; 3) scopolamine; and 4) combined scopolamine and mecamylamine on four separate days. At the time of peak drug concentration, Pulsed-continuous arterial spin labeling (PCASL) (4) CBF images were acquired with 3D spiral RARE sequence. Cognitive testing was performed with a neuropsychological battery (5).

Brain CBF images were quantified using the CBF kinetic model (6,7). Images were analyzed using SPM2 software. All perfusion images (from the 4 pharmacologic conditions) from each subject were motion corrected, normalized to a standard MNI brain space and smoothed using 8-mm Gaussian kernel. A general linear model with 15 subjects and 4 conditions was used to identify the regions with significant perfusion changes caused by mecamylamine and scopolamine. Cluster level analysis was performed and corrected for family-wise error (FWE) caused by multiple comparisons. The corrected cluster-level p value threshold was 0.05 with voxel-level p value of 0.05. Cognitive performance was analyzed with repeated measures ANOVA.

Results

With scopolamine, CBF was decreased bilaterally in thalamus, frontal cortex, and supplementary motor area and increased in occipital cortex, postcentral gyrus, insula, hippocampus, and superior temporal pole (Fig. 1). With mecamylamine, CBF was decreased in cerebellum, precuneus, cuneus, lingual, vermis and calcarine and increased in putamen, postcentral,insula, frontal, precentral and parietal regions (Fig. 2). No significant interaction term was observed. Compared to placebo, participants performed worse on memory (Selective Reminding Test, $p<0.01$) and visual attention (Trails B, $p<0.05$) with scopolamine.

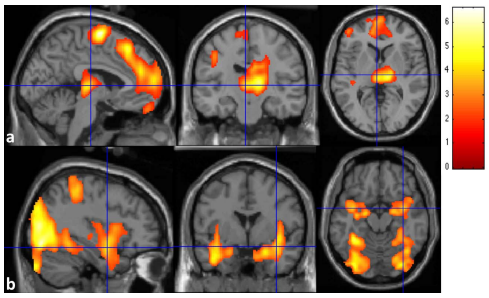
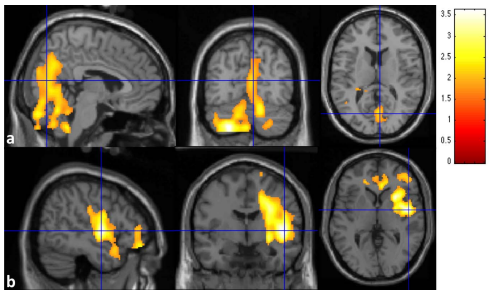


Fig 1 (left). Statistically significant regions overlaid on the structural images with administration of scopolamine for (a) decreased CBF and (b) increased CBF.

Fig 2 (right). Statistically significant regions overlaid on the structural images with administration of mecamylamine for (a) decreased CBF and (b) increased CBF.



Discussion

These results confirm previous findings of decreased frontal and thalamic perfusion and cognitive deficits with scopolamine and reveal other areas implicated in cognition with cholinergically modulated blood flow, suggesting that ASL may be more sensitive to the perfusion changes under study. The cognitive impairments with cholinergic blockade, including impaired attention and encoding, are consistent with disruption of the attention network. Likewise memory deficits could result from disruption of known memory structures (eg. hippocampus) or decreased activity of inhibitory thalamic projections to cortical structures.

References: 1. Fibiger et al, Adv Exp Med Biol 1991;295:399-414 2. Blokland et al, Brain Res Brain Res Rev 1995;21(3):285-200. 3. Tariot et al, Psychopharmacology 1996;125(1):50-6 4. Dai et al, Magn Reson Med 2008;60(6):1488-1497. 5. Little et al, Neuropsychopharmacology 1998:19(1):60-9. 6. Buxton et al, Magn Reson Med 1998;40:383-396. 7. Alsop et al, Journal of Cerebral Blood Flow and Metabolism 1996;16:1236-1249.