Effects of scopolamine on MEG spectral power and coherence in elderly subjects

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Abstract

Objective: Scopolamine, a muscarinic receptor antagonist, can produce temporary cognitive impairments as well as electroencephalographic changes that partially resemble those observed in Alzheimer’s disease. In order to test the sensitivity of spectral power and hemispheric coherence to changes in cholinergic transmission, we evaluated quantitative magnetoencephalogram (MEG) after intravenous injection of scopolamine.

Methods: MEG of 8 elderly healthy subjects (59–80 years) were measured with a whole-head magnetometer after intravenous injection of scopolamine. An injection of glycopyrrolate, a peripheral muscarinic antagonist, was used as the placebo in a double-blind, randomized, cross-over design. Spectral power and coherence were computed over 7 brain regions in 3 frequency bands.

Results: Scopolamine administration increased theta activity (4–8 Hz) and resulted in the abnormal pattern of MEG desynchronization in eyes-open vs. eyes-closed conditions in the alpha band (8–13 Hz). These effects were most prominent over the posterior regions. Interhemispheric and left intrahemispheric coherence was significantly decreased in the theta band (4–8 Hz).

Conclusions: Spontaneous cortical activity at the theta and alpha range and functional coupling in the theta band are modulated by the cholinergic system. MEG may provide a tool for monitoring brain dynamics in neurological disorders associated with cholinergic abnormalities.

Keywords: Scopolamine; Magnetoencephalogram; Spectral power; Coherence; Aging; Acetylcholine

1. Introduction

Ascending cholinergic pathways, constituted by the two main projection systems from the basal forebrain to the neocortex and from the reticular formation to the thalamus, are thought to play an important role in the modulation of spontaneous cortical electromagnetic rhythms (Shute and Lewis, 1967) and higher cognitive functions, such as memory and attention (Mesulam, 1987; Goto et al., 1990). Acetylcholine application in vivo and in vitro decreases potassium conductance and thus, has an excitatory influence on neocortical cells, enhancing their responsiveness to afferent input and causing electroencephalographic (EEG) desynchronization (for review, see Steriade et al., 1990). Decrease of cholinergic markers, presumably associated with deficits in cholinergic pathways, is, in turn, related to the progressive decline of cognitive skills (Small and Mayeux, 2000) and abnormalities in spontaneous EEG activity in, for instance, Alzheimer’s disease (AD; Coben et al., 1983; Penttilä et al., 1985). In healthy subjects, the effect of acetylcholine can be blocked by muscarinic receptor antagonist, scopolamine, that produces transient...
cognitive deficits (Sunderland et al., 1986; Broks et al., 1988) and EEG/MEG changes (Sannita et al., 1987; Neufeld et al., 1994), resembling those observed in AD. Therefore, scopolamine has been suggested as a psychopharmacological model of AD (for review, see Ebert and Kirch, 1998).

Quantitative EEG studies with scopolamine have revealed slowing of spontaneous cortical activity, which manifests itself in decreased alpha (Sannita et al., 1987; Neufeld et al., 1994; Ebert et al., 1998) power and increased theta (Sannita et al., 1987) and delta (Sannita et al., 1987; Neufeld et al., 1994; Ebert et al., 1998) power. Many components of auditory and somatosensory magnetic evoked responses in healthy subjects appear to be modulated by cholinergic transmission as well (Ahveninen et al., 1999, 2002; Jääskeläinen et al., 1999; Pekkonen et al., 2001; Huttunen et al., 2001). Previous studies have also indicated that scopolamine administration may affect resting corticocortical EEG coherence, which reflects functional brain connectivity based on synchronization between two signals at different scalp locations (Sloan et al., 1992; Kikuchi et al., 2000). Sloan et al. (1992), for example, reported the scopolamine-induced decrease of interhemispheric EEG coherence in alpha and beta bands, while Kikuchi et al. (2000) found coherence reduction in delta and beta-1 ranges. The fact that no coherence analyses were made with scopolamine in elderly subjects might reduce the relevance of these results to pharmacological modeling of dementia.

MEG is a convenient non-invasive brain-imaging method with millisecond temporal resolution and spatial resolution exceeding that of conventional EEG (for review, see Hämäläinen et al., 1993). Good replicability of MEG spontaneous activity has been demonstrated regarding, at least, alpha rhythm (Ciulla et al., 1999). In addition, MEG, as a reference-free method, can eliminate possible inaccuracies in the coherence analyses, caused by the choice of the reference (Fein et al., 1988).

Given the lack of information on acetylcholine modulation of spontaneous MEG power spectrum and coherence in aged subjects, we used a 122-channel MEG device to study the cholinergic modulation of MEG power spectrum and inter- and intrahemispheric coherence in elderly subjects. We expected that administration of scopolamine to elderly subjects would produce the effects partially similar to those observed in AD. As a reference drug, we used glycopyrrolate, a peripheral muscarinic receptor antagonist that does not penetrate the blood–brain barrier.

2. Methods

2.1. Subjects

The study was accepted by the National Agency for Medicine and the Ethics Committee of the local University Hospital. A written informed consent was obtained from all the subjects after a detailed explanation of the procedures. Eight healthy right-handed volunteers (59–80 years; 6 females) were recruited by E.P. from a community cultural center for elderly citizens. Subjects were intravenously given either scopolamine hydrobromide (0.3 mg) or glycopyrrolate (0.2 mg) in a double-blind, cross-over design. The drugs were administered 1 h before the measurements and the subjects were supervised for at least 8 h after the drug administration (by a trained nurse or physician). All subjects had no history of neurological or psychiatric disorders; none of them reported using drugs affecting the central nervous system. The subjects were instructed to avoid alcohol for at least 48 h and caffeine and tobacco for 12 h before the recordings. All recordings were conducted between 8 a.m. and 12 a.m. with 1 week interval between the sessions to minimize the possible effects of circadian rhythms.

2.2. MEG recording

The subjects were seated comfortably in a magnetically shielded room (Euroshield, Eura, Finland) with the head inside a 122-channel whole-head MEG device (Neuromag Ltd, Finland). Spontaneous activity was recorded for 120 s with eyes open and for 120 s with eyes closed (pass-band 0.03–150 Hz, sampling rate 400 Hz).

2.3. Data analysis

Off-line artifact rejection was performed with all epochs containing amplitudes over 3 pT/cm being rejected as containing extra-cerebral artifacts. An average of 35 (minimum 21, maximum 50) epochs, each 2.56 s, were subjected to spectral analysis by Fourier transformation. Power spectra were calculated for each of the 122 channels, then power spectra averages over 8 channels blindly selected from 7 brain regions (frontal, central, left temporal, right temporal, left parietal, right parietal, and occipital) were calculated for both scopolamine and glycopyrrolate conditions. Next, averaged power in theta (4–8 Hz), alpha (8–13 Hz), and beta (13–22 Hz) bands was calculated. Logarithmic transformation was applied to the power data prior to statistical analysis. To eliminate variability caused by the differences in individual spectral power, the eyes closed/eyes open ratio was calculated for both drug sessions separately. Coherence values were calculated as cross-correlation normalized by power spectra between the channels (4-D Toolbox, Ole Jensen, 2000). In order to compute the coherence, one artifact-free channel was selected from central, parietal, temporal, and occipital regions of each hemisphere. Coherence was calculated in the same frequency bands as power spectra. Interhemispheric coherence was computed between the channels located in the corresponding regions of the two hemispheres and intrahemispheric coherence was calculated between the selected channel pairs within each hemisphere with
the subsequent Fisher’s z-transformation. A 3-way repeated measures ANOVA (drug by eyes closed/open by region) followed by a series of paired t tests was carried out in each of the frequency bands to test drug effect on power and to compare the eyes opening ratio within both drug conditions. Coherence was similarly compared between the drug sessions using 3-way repeated measures ANOVA (drug by eyes closed/open by channel pair). All comparisons of means were Bonferroni-corrected.

3. Results

ANOVA indicated a significant increase of power induced by scopolamine ($F(1,7) = 6.79, p < 0.05$), significant drug by eyes ($F(1,7) = 9.42, p < 0.05$), and drug by region ($F(6,42) = 2.44, p < 0.05$) interaction in the theta band. No significant drug effect was found in other frequency bands, although significant drug by eyes interaction was observed in alpha ($F(1,7) = 8.21, p < 0.05$) and beta ($F(1,7) = 6.44, p < 0.05$) bands. Drug by region interaction was also significant in the alpha band ($F(6,42) = 3.02, p < 0.05$). Paired t tests showed a significant increase of theta power in the left parietal ($p < 0.05$) region in the eyes-open condition.

Eyes closed/open ratio, disclosing eyes by drug interaction, was significantly reduced in the theta ($F(1,7) = 11.48, p < 0.05$), alpha ($F(1,7) = 9.56, p < 0.05$), and beta ($F(1,7) = 6.6, p < 0.05$) bands. Drug by region interaction was significant for the ratio in the theta ($F(6,42) = 3.37, p < 0.01$) and alpha ($F(6,42) = 3.52, p < 0.01$) bands. Paired t tests showed a significant decrease of the ratio in the right temporal region in the theta band ($p < 0.05$). The reduction of eyes closed/open ratio is presented in Fig. 1. The differences in the eyes closed/open coefficient between the drug conditions were the greatest in the alpha band, which suggests scopolamine-induced lack of MEG desynchronization associated with eyes opening (Fig. 1). The effect was more prominent in the posterior regions.

In the coherence analysis, ANOVA revealed a significant scopolamine-induced reduction of interhemispheric ($F(1,7) = 10.31, p < 0.05$) and left intrahemispheric ($F(1,7) = 19.69, p < 0.01$) coherence in the theta band. The drug by eyes ($F(1,7) = 22.99, p < 0.01$) and drug by channel pair ($F(3,21) = 4.9, p < 0.01$) interactions were
significant for interhemispheric coherence in the theta band. Significant drug by eyes interaction was also revealed for the interhemispheric coherence in the alpha band \((F(1,7) = 6.16, \ p < 0.05)\). No significant effects were found in the beta band. The coherence values are presented for theta and alpha bands in Table 1.

Finally, as for the self-reported subjective effects of the drugs, scopolamine administration had no major side effects but some of the subjects reported slight dizziness.

4. Discussion

The administration of scopolamine, a central antagonist of muscarinic acetylcholine receptors, evoked an abnormal pattern of MEG desynchronization/synchronization. One of the most substantial effects of scopolamine was the overall reduction of the eyes closed/open ratio. The reduction of the ratio was the most prominent in the alpha band, which suggests the lack of desynchronization, normally associated with the eyes opening. In addition, a significant increase of MEG power was observed in the theta band. Finally, significant scopolamine-induced reduction of interhemispheric and left hemisphere coherence was observed in the theta band (4–8 Hz). These results suggest at least partial modulation of spectral power and corticocortical coherence by muscarinic cholinergic transmission.

4.1. Spectral power

Although the eyes closed/open ratio was reduced throughout all frequency bands, the most essential differences were found in the alpha range. The reduced ratio demonstrates greater MEG synchronization in the eyes-open condition after scopolamine administration, revealing abnormalities in the pattern of spontaneous MEG activity. The observed phenomenon could be attributed to the fact that scopolamine, being a central muscarinic receptor antagonist, interferes with the thalamocortical circuits possibly blocking post-synaptic receptors (Deutsch, 1971). This probably reduces the action of acetylcholine and may produce synchronized cortical oscillations, observed after scopolamine administration and being more prominent in the eyes-open condition.

Theta power was significantly increased after scopolamine administration in both eyes closed and eyes-open conditions, which also supports previous EEG results (for review, see Ebert and Kirch, 1998). Similar to the alpha power, the reduction of the eyes closed/open ratio in the theta band indicates the increase of slow-wave activity in the eyes-open state. Intensive in vivo studies in rodents, for instance, have revealed an important role of septohippocampal structures in theta generation (Bland and Oddie, 1998; Keita et al., 2000), which is particularly interesting in the light of the well-documented hippocampal atrophy in

Table 1

<table>
<thead>
<tr>
<th>Coherence</th>
<th>Channel pair</th>
<th>Theta</th>
<th>Alpha</th>
<th>Beta</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Glycopyrrolate</td>
<td>Scopolamine</td>
<td>Glycopyrrolate</td>
</tr>
<tr>
<td>Eyes closed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>Temporal–central</td>
<td>0.10 ± 0.09</td>
<td>0.11 ± 0.08</td>
<td>0.11 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Temporal–parietal</td>
<td>0.09 ± 0.10</td>
<td>0.13 ± 0.10</td>
<td>0.12 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>Temporal–occipital</td>
<td>0.10 ± 0.07</td>
<td>0.09 ± 0.06</td>
<td>0.10 ± 0.08</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>Temporal–central</td>
<td>0.13 ± 0.04</td>
<td>0.10 ± 0.05</td>
<td>0.12 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>Temporal–parietal</td>
<td>0.13 ± 0.06</td>
<td>0.14 ± 0.07</td>
<td>0.17 ± 0.09</td>
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<tr>
<td></td>
<td>Temporal–occipital</td>
<td>0.15 ± 0.11</td>
<td>0.09 ± 0.04</td>
<td>0.13 ± 0.08</td>
</tr>
<tr>
<td>Interhemispheric</td>
<td>Temporal–temporal</td>
<td>0.09 ± 0.07</td>
<td>0.04 ± 0.03</td>
<td>0.06 ± 0.05</td>
</tr>
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<td></td>
<td>Central–central</td>
<td>0.03 ± 0.02</td>
<td>0.03 ± 0.02</td>
<td>0.07 ± 0.03</td>
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<tr>
<td></td>
<td>Parietal–parietal</td>
<td>0.02 ± 0.01</td>
<td>0.03 ± 0.01</td>
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<td></td>
<td>Occipital–occipital</td>
<td>0.15 ± 0.08</td>
<td>0.13 ± 0.08</td>
<td>0.16 ± 0.09</td>
</tr>
<tr>
<td>Eyes open</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>Temporal–central</td>
<td>0.10 ± 0.09</td>
<td>0.11 ± 0.09</td>
<td>0.12 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>Temporal–parietal</td>
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<td>0.13 ± 0.10</td>
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<td></td>
<td>Temporal–occipital</td>
<td>0.09 ± 0.07</td>
<td>0.09 ± 0.07</td>
<td>0.09 ± 0.05</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>Temporal–central</td>
<td>0.15 ± 0.03**</td>
<td>0.09 ± 0.05</td>
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<td></td>
<td>Temporal–parietal</td>
<td>0.12 ± 0.05</td>
<td>0.13 ± 0.07</td>
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</tr>
<tr>
<td></td>
<td>Temporal–occipital</td>
<td>0.18 ± 0.15</td>
<td>0.10 ± 0.06</td>
<td>0.16 ± 0.11</td>
</tr>
<tr>
<td>Interhemispheric</td>
<td>Temporal–temporal</td>
<td>0.10 ± 0.07*</td>
<td>0.05 ± 0.03</td>
<td>0.05 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>Central–central</td>
<td>0.04 ± 0.03</td>
<td>0.03 ± 0.02</td>
<td>0.08 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>Parietal–parietal</td>
<td>0.04 ± 0.02</td>
<td>0.02 ± 0.01</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>Occipital–occipital</td>
<td>0.19 ± 0.12</td>
<td>0.11 ± 0.10</td>
<td>0.16 ± 0.12</td>
</tr>
</tbody>
</table>

Paired \(t\) tests showed no significant effects in other frequency bands.

*\(p < 0.05\); **\(p < 0.01\).
AD (Small and Mayeux, 2000). MEG, however, predominantly measures neocortical activity (Hämäläinen et al., 1993) and thus, the medial–temporal structures might not be the primary source of the theta power decrease induced by a blockade of muscarinic receptors. Therefore, the neural basis of the present results will have to be confirmed by further efforts. Nevertheless, there is also evidence that neocortical circuitry, which produces activity detected by MEG, may also participate in theta generation, as it was shown in rats (Landfield and McGaugh, 1972; Lukatch and Maciver, 1997).

Notably, the observed increase of synchronized activity resemble EEG and MEG findings in AD (Signorino et al., 1995; Berendse et al., 2000; Stevens et al., 2001). In addition, scopolamine-induced power changes in the theta band were more prominent in the temporal and parietal regions, which is consistent with EEG (Miyauchi et al., 1994; Wada et al., 1997) and MEG (Fernandez et al., 2002) studies of AD. Although the topography of changes caused by scopolamine administration is thought to differ from regional abnormalities observed in AD (Honer et al., 1988), our data are obtained from the elderly population, which possibly makes cholinergic deficits more pronounced.

4.2. Corticocortical coherence

Administration of scopolamine altered resting coherence, suggesting transient changes in functional integrity of the brain (Lopes da Silva, 1993). We demonstrated a significant reduction of coherence in the theta band, which was also found in previous studies on dementia (Besthorn et al., 1994; Wada et al., 1998; Berendse et al., 2000; Knott et al., 2000). Scopolamine thus produced the coherence effects similar to the state of cerebral degeneration in AD, which has been shown to increase the time of information propagation (Besthorn et al., 1994). Interestingly, theta coherence was reduced over the left, but not over the right hemisphere. The effect was more pronounced in the eyes-open condition, as indicated by the drug by eyes interaction both in theta and alpha bands. As a matter of fact, scopolamine induced the decrease of coherence accompanying eyes opening, while glycopyrrolate produced the opposite effect. Future studies are needed to elucidate the neural basis of this finding.

In contrast to our results, the two previous EEG studies with scopolamine (Sloan et al., 1992; Kikuchi et al., 2000) found no decrease in the theta range in young healthy volunteers. Given the MEG sensitivity to cortical activity, our results might reflect specific cortical pattern of scopolamine-modulated coherence in elderly subjects. Additionally, drug dose and administration type differed between the studies. The pharmacodynamic effect of scopolamine is different for intramuscular (Kikuchi et al., 2000), subcutaneous (Sloan et al., 1992), and intravenous administration, the latter used in the present study. On the other hand, the decrease of alpha and beta coherence shown in the aforementioned studies was not consistent in our results.

5. Conclusions

Scopolamine induced an increase of synchronized oscillations and coherence reduction in the theta range in aged healthy subjects. These oscillatory deficits appear to be modulated by cholinergic transmission and partially resemble those observed in AD. Thus, MEG may provide an efficient tool for detecting cortical changes of the cholinergic activity in neurodegenerative diseases, such as AD.

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