Visual evoked potential and electroencephalogram of healthy females during the menstrual cycle

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Abstract: Flash visual evoked potential (VEP) and electroencephalogram (EEG) changes during the menstrual cycle were studied using healthy females having regular menstruation, with 21 at the follicular phase (FP) and 23 at the luteal phase (LP). The following results were obtained. (1) The waveforms of Group Mean VEPs of both groups had approximately similar triphasic contours, consisting of 16 components of P1-N8 up to 500 msec of latency. (2) Latencies tended to be longer in LP. (3) Interpeak amplitudes tended to be larger in LP, and one VEP interpeak amplitude (P5-N7) of long latency component was significantly larger at LP after eliminating the effect of body height by ANCOVA for 2 CH. (4) Quantitative analysis of EEGs between FP and LP resulted in a tendency for increased α, and decreased β power % at LP. Since estrogen increases the VEP amplitude, and decreases the VEP latency and the α activity of EEGs, the large VEP amplitude, the tendency for prolonged VEP latency, and the tendency for increased α power % at LP observed in this study indicate that the VEP amplitude at LP reflects the effect of estrogen, and that the VEP latency and EEGs at LP reflect the effect of progesterone. J. Med. Invest. 44: 41-46, 1997

Key Words: visual evoked potential, electroencephalogram, menstrual cycle, estrogen, progesterone

INTRODUCTION

Visual evoked potentials (VEPs) provide information regarding the central nervous system (CNS) including the visual system and brain excitability (10), and are often used in clinical neurophysiology (13, 23, 30). Variabilities in VEP amplitudes and latencies are the main criteria of pathology. VEP latencies are shorter and amplitudes are larger in females than in males in the normative data (1, 4, 15, 27, 33). In addition, in our previous study using 100 females and 100 males, the same result was verified not only in the shorter or middle latency components (up to 240 msec), but also in the longer latency components (up to 500 msec) (15).

In females, the mood (11, 34) or psychometric performance (6) changes in normal women has been reported during normal menstruation, and some neurophysiologic studies have demonstrated electroencephalogram (EEG) changes with the menstrual cycle (6, 35). However, there have been few reports of VEP changes during the menstrual cycle (22, 29), and they related only to the shorter or middle latency components (up to 240 msec). Therefore, in the present study, the statistical differences in VEPs of females, including those of later components (up to 500 msec) were studied between FP and LP, using 44 subjects out of 100 having regular menstrual cycles.

MATERIALS AND METHODS

1. Materials

The subjects in the present study were 44 female students (paid volunteers) who had regular menstrual cycles. Of them, twenty-one were at the follicular phase (FP) (generally day 1-13 of a 28-day cycle, when estrogen alone is raised) at the time of recording, and the remaining 23 were at the luteal phase (LP) (generally day 15-28, when estrogen and progesterone are raised). Average body height was significantly greater at FP than at LP, but average body weight or age was not (t-test, p<0.05) (Table 1). All subjects had no neuropsychiatric history, visual disorders or ongoing medication. EEGs of all subjects were within the normal range. One out of 21 females at FP and 2 out of 23 females at LP were left-handed.

2. Recording methods of VEPs and EEGs

Recording electrodes were placed on the scalp according to the international 10-20 system, in preference to

<table>
<thead>
<tr>
<th>N</th>
<th>Age (yr) Mean±SD</th>
<th>Body Height (cm) Mean±SD</th>
<th>Body Weight (kg) Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP</td>
<td>21 21.6±2.4</td>
<td>160.1±4.9</td>
<td>51.4±5.5</td>
</tr>
<tr>
<td>LP</td>
<td>23 21.1±2.0</td>
<td>156.6±4.1</td>
<td>51.4±5.6</td>
</tr>
<tr>
<td>t-test</td>
<td></td>
<td></td>
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<tr>
<td>Total 44</td>
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(FP: follicular phase, LP: luteal phase, *p<0.05)

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linked ear lobes. Electrode impedance was kept below 5 kΩ. While recording, the subjects laid, with eyes closed, in a reclining chair at 70 degrees in a dark shielded room, at 24-25°C. The consciousness level of subjects was monitored by EEG. Flash stimuli from the XENON tube of acoustically shielded Retinograph MSP-2 R (Nihon Kohden) were presented from a distance of 30 cm once every 5 sec. The intensity of the flash was 0.6 J.

EEGs containing VEPs were derived from the two derivations, 2 CH (O1→A1-) and 5 CH (O1→C3) (28), amplified by Preamplifier AB-622 M with 0.1 sec time constant, with 100 Hz high range filter and without using a hum eliminating filter. Data were recorded by Data Recorder RX-50 L (TEAC) onto magnetic tapes with trigger pulses synchronized to the flash stimuli.

Reproducing EEGs and trigger pulses from the tape by Data Recorder RX-50 L, VEPs derived through the two derivations of each subject were recorded by averaging 100 single responses by ATAC-210 (1024 address×231 bit) for 1024 msec of analysis time.

3. Methods of data processing
3·1 Data processing of VEPs

VEPs were processed by subsequent computation. Each VEP was adjusted by least squares so that sums of squares of instantaneous values from the baseline were minimum.

3·1·1 Group Mean VEPs

The group Mean VEPs for each group were obtained for 2 CH and 5 CH, respectively. The components (P 1-P 8, N 1-N 8) in Group Mean VEPs were identified on a CRT monitor. The differences in the waveforms, latencies and interpeak amplitudes of Group Mean VEPs between FP and LP were compared for each derivation.

3·1·2 Individual VEPs

Referring to the components in Group Mean VEPs, those in Individual VEPs were identified on a CRT monitor, respectively for each derivation. The differences in the latencies and interpeak amplitudes of Individual VEPs between FP and LP were compared and tested by t-test, and by analysis of covariance (ANCOVA) with reference to body height for each derivation.

3·2 Data processing of EEGs

Absolute power values of EEGs were calculated with the program (QP-130 B "RHYTHM") by quantitative frequency analysis. Eight epochs (32 sec) with 128 Hz sampling rate and 512 points were analyzed every 0.25 Hz by fast Fourier transformation. Through division into 6 frequency bands, δ (2.0-3.75 Hz) and θ (4.0-7.75 Hz), α 1(8.0-9.75 Hz), α 2 (10.00-12.75 Hz), β 1 (13.00-19.75 Hz), β 2 (20.00-30.00 Hz), absolute amplitudes and power % of each band were calculated. Then, the average absolute amplitudes and average power % were compared and tested between FP and LP by t-test for each derivation.

RESULTS

1. Waveforms of Group Mean VEPs of each group

The waveforms of Group Mean VEPs of each group were approximately triphasic up to 500 msec in latency for both 2 CH and 5 CH, and consisted of 16 components, P 1, N 1, P 2, N 2, P 3, N 3, P 4, N 4, P 5, N 5, P 6, N 6, P 7, N 7, P 8 and N 8 (Fig.1). The highest positive peak of each Group Mean VEP was P 5 in both FP and LP for both derivations. The lowest negative peaks were N 3 in both FP and LP for 2 CH, N 8 at FP and N 7 at LP for 5 CH. The maximal interpeak amplitudes of Group Mean VEPs (2 CH : N 3-P 5, 5 CH : P 5-N 7) were larger at LP than in FP.

2. Component analysis for Individual VEPs

2·1 Waveforms of Individual VEPs

The waveforms of Individual VEPs were similar to those of Group Mean VEPs derived from the same derivations. The appearance rates of each component varied from 67 to 100 % (Table 2). Five peaks (N 3, P 5, N 7-N 8) at FP, and eight peaks (P 2, N 3, P 5, N 6-N 8) at LP for 2 CH, six peaks (P 2-N 3, P 5 and N 8) at FP, and eight peaks (N 2-N 3, P 5, P 7-N 8) at LP for 5 CH were consistently identified. The prominent interpeak amplitudes of VEPs at LP for 2 CH (N 3-P 5) and for 5 CH (P 5-N 7) were 7 %

![Fig. 1. Group Mean VEPs in 21 Females at FP and in 23 Females at LP. Scales of amplitude are comparative, 128.7 corresponding to 50 μV.](image-url)
and 9% larger, respectively, than those at FP (N 3-P 5 for 2 CH, P 4-N 8 for 5 CH).

2.2 Differences in Individual VEP components between FP and LP

2.2.1 Differences in Individual VEP latencies between FP and LP

The VEP latencies of 9 components were shorter at LP than at FP for 2 CH (Table 2). The latency of P 3 was significantly shorter at LP than at FP, and that of P 2 was significantly longer at LP for 2 CH by t-test (p<0.05). After eliminating the effect of body height, these differences were not significant by ANCOVA.

Although eleven latencies were longer at LP than at FP for 5 CH, the differences were not significant by t-test nor ANCOVA (Table 2).

2.2.2 Differences in Individual VEP interpeak amplitudes between FP and LP

Thirteen out of 23 VEP interpeak amplitudes including

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### Table 2. Latencies (msec) of Individual VEPs at FP and LP

<table>
<thead>
<tr>
<th></th>
<th>2 CH</th>
<th></th>
<th>5 CH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FP</td>
<td>LP</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>13.7</td>
<td>15.6</td>
<td>15.9</td>
</tr>
<tr>
<td>SD</td>
<td>3.2</td>
<td>4.4</td>
<td>4.9</td>
</tr>
<tr>
<td>CV</td>
<td>23.7</td>
<td>28.3</td>
<td>33.7</td>
</tr>
<tr>
<td>N</td>
<td>14</td>
<td>20</td>
<td>19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2 CH</th>
<th></th>
<th>5 CH</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>FP</td>
<td>LP</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>15.2</td>
<td>13.4</td>
<td>18.2</td>
</tr>
<tr>
<td>SD</td>
<td>5.0</td>
<td>4.5</td>
<td>3.7</td>
</tr>
<tr>
<td>CV</td>
<td>32.9</td>
<td>33.7</td>
<td>29.4</td>
</tr>
<tr>
<td>N</td>
<td>19</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>

### Table 3. Interpeak Amplitudes (μV) of Individual VEPs at FP and LP

<table>
<thead>
<tr>
<th></th>
<th>2 CH</th>
<th></th>
<th>5 CH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>77.4</td>
<td>130.1</td>
<td>58.1</td>
</tr>
<tr>
<td>SD</td>
<td>39.9</td>
<td>306.0</td>
<td>68.9</td>
</tr>
<tr>
<td>CV</td>
<td>94.9</td>
<td>228.7</td>
<td>36.9</td>
</tr>
<tr>
<td>N</td>
<td>46.2</td>
<td>22.8</td>
<td>4.9</td>
</tr>
</tbody>
</table>

(1) Result of testing of differences by t-test
(2) Result of testing of differences, from which effect of body height was eliminated, by ANCOVA

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(1) p<0.05, (2) p<0.005

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the prominent interpeak amplitude were larger at LP than at FP for 2 CH (Table 3). The interpeak amplitude of P 5–N 7 was significantly larger at LP than at FP for 2 CH by t-test (p<0.01), even after eliminating the effect of body height by ANCOVA (p<0.05).

Although eighteen interpeak amplitudes including the prominent interpeak amplitude were larger at LP for 5 CH, the difference was not significant by t-test nor ANCOVA (Table 3).

3. Differences in EEGs by quantitative frequency analysis between FP and LP

3 · 1 EEG absolute amplitudes and their differences between FP and LP

There was no significant difference in EEG absolute amplitudes between FP and LP in either derivation by Mann Whitney's U-test (Table 4).

3 · 2 EEG power % and their differences between FP and LP

Although there was a tendency for increased α, and decreased β power % in LP, there was no significant difference in EEG power % between FP and LP in either derivation by Mann Whitney's U-test (Table 4).

DISCUSSION

In general, shorter people tend to have a smaller brain (31), and to have shorter VEP latency (1, 15). However, latency tended to be longer at LP in the present study, though there were no significant latency differences after eliminating the effect of body height by ANCOVA. This result is consistent with the previous report by Simpson, et al. (29). Physical conditions such as relaxed state (8), sleep (5), and neuroendocrinological factors such as estrogen (7, 25) and progesterone (25) are supposed to affect VEP latency both at FP and LP. The consciousness level of the subjects was monitored by EEG to be awake during recording. FP is a period when estrogen alone is raised, and LP is a period when both estrogen and progesterone are raised. The effects of estrogen on the CNS are likely to be antagonized by progesterone and its metabolites (17, 25). In addition, estrogen has been shown to shorten the latency of VEPs in animals (7, 25), whereas progesterone prolongs latency (25). Therefore, the tendency for the prolonged VEP latency at LP is thought to reflect the effect of progesterone more than estrogen.

In the present study, VEP amplitudes of long components (up to 500 msec), tended to be larger at LP. Moreover, there was a significantly larger amplitude (P 5–N 7 for 2 CH) at LP than at FP after eliminating the effects of body height by ANCOVA (p<0.05). This result is consistent with other studies of VEPs (22, 29) or ERPs (19). Physical conditions such as relaxed state (8), attention (21), sleep (5) or body temperature (2), and neuroendocrinological factors such as estrogen (7, 25) and progesterone (25) are supposed to affect VEP amplitude both at FP and LP. Increased body temperature reduces the amplitude of the VEP (2), and lower temperature increases compound action potential amplitude (3). However, averaged body temperature is reported to be higher at LP than at FP (9). Therefore, the difference in body temperature is unlikely to account for the observed amplitude differences.

Lehtonen et al. (22) suggested the correlation between increased VEP amplitude at LP (22) and increased photic driving in EEGs (35), which is thought to reflect central adrenergic processes (36). However, increased VEP amplitude at LP does not correlate with increased photic driving in EEGs. In animals, VEP amplitude has been shown to be increased by estrogen (7, 25) directly and/or indirectly through L-type voltage-dependent calcium channels (12), acetylcholine (16), monoamines (18, 20), γ-aminobutyric acid (24, 26, 32) or glutamate (32), and to be inhibited by progesterone (25) directly and/or indirectly through γ-aminobutyric acid or glutamate (32). In humans, photic driving has been shown to be reduced by estrogen (18, 35) and to be enhanced by progesterone (35). Therefore, larger VEP amplitude at LP observed in the present and previous studies (22, 29) indicates that VEP amplitude at LP reflects the effect of estrogen more than progesterone, while increased photic driving in EEGs at LP (35) indicates that EEGs at LP reflect the effect of progesterone more than estrogen.

Table 4. Quantitative Frequency Analysis of EEGs at FP and LP

<table>
<thead>
<tr>
<th>Frequency bands (Hz)</th>
<th>2 CH</th>
<th>5 CH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute amplitude (μV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td>12.6±6.4</td>
<td>7.8±3.5</td>
</tr>
<tr>
<td>LP</td>
<td>11.9±7.8</td>
<td>7.9±3.9</td>
</tr>
<tr>
<td>U-test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Power % (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td>6.0±3.0</td>
<td>6.0±3.0</td>
</tr>
<tr>
<td>LP</td>
<td>5.8±3.3</td>
<td>5.8±3.3</td>
</tr>
<tr>
<td>U-test</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the present study, although no significant differences were seen in EEGs by quantitative frequency analysis between FP and LP in both their absolute amplitudes and power % of each band, there was a tendency for increased \( \alpha \) power % at LP. This result was consistent with other studies (6). In addition, Creutzfeldt, et al. (6) reported the slight decrease of \( \theta \) power at LP, and our data shows a tendency for decreased \( \beta \) power % at LP. In a study of estradiol 17-\( \alpha \)-valerate, the valerate-acid ester of the endogenous female estrogen, according to the power spectral analysis of EEG, an increase of slower as well as faster waves and a decrease of the activities 9 to 12 cps were demonstrated (14). Therefore, as Creutzfeldt, et al. (6) founded, EEG findings in this study also indicate that EEGs at LP reflect the effect of progesterone more than estrogen.

In conclusion, the large VEP amplitude, and the tendency for increased \( \alpha \) power % and at LP verified in this study were considered to indicate that the VEP amplitude at LP reflects the effect of estrogen more than progesterone, and that the VEP latency and EEG changes at LP reflect the effect of progesterone more than estrogen. We believe that VEP analysis is a useful tool for the study of the actions of gonadal hormones on CNS, not only in animals but also in humans.

ACKNOWLEDGMENTS

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