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LONG LATENCY AUDITORY EVOKED RESPONSES IN OVULATORY AND ANOVULATORY MENSTRUAL CYCLE

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Abstract : Central nervous system pathways get influenced by the changing hormonal levels across the menstrual cycle. In an effort to see the effects on the conduction in central auditory pathways we recorded long latency auditory evoked potentials (LLAEPs) across the 4 different phases of the menstrual cycle. 20 females having normal ovulatory menstrual cycles were tested 4 times in a single cycle and LLAEPs were recorded from Cz-A1 and Cz-A2 position with alternating 90 dB sound pressure click stimuli. Twenty age matched control females having anovulatory menstrual cycles were also tested on the corresponding days. All control females were taking oral contraceptive (O.C.) pills. The LLAEPs were compared inter-group wise as well as inter-phase wise for each parameter by using hierarchal ANOVA design and Tukey test was applied to find out the significance level.

Peak latencies of waves P2 and N2 were found to be delayed during mid-cycle and relatively reduced mid-luteal phase in ovulatory menstrual cycles. No such response was noticed in oral contraceptive using group. This indicates that normal cyclic variations of female sex hormones especially estrogen and progesterone modify the central processing of the auditory information. Estrogen may be responsible for delaying the conduction by influencing GABA release at the level of polysensory association areas of the brain.

Key words : LLAEPs menstrual cycle oral contraceptives estrogen progesterone evoked responses

INTRODUCTION

Ovarian hormones have long been known to affect the sensory information processing in the brain (1, 2). Auditory perception being one of the sensory modality also gets influenced by sex hormones. For many years it has been known that females have better hearing threshold and it has been attributed to the influence of female sex hormones specially estrogen and progesterone (3, 4). Evaluation has already been done by using Brainstem Auditory Evoked Responses (BAER) in different phases of the menstrual

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cycle. Some researchers have reported no change across the menstrual cycle (5–7) while others have reported delayed conduction during mid- cycle and faster conduction during mid-luteal phase (8–11). Waves from the increasingly rostral brain sites were found to be affected most (12). No report is available indicating the effects of sex hormones on the higher centers of auditory pathways. So we planned to record long latency responses in an effort to see those effects using non-invasive electrophysiological tools.

Long latency Auditory Evoked Potential (LLAEP) is an important tool to assess the auditory information processing at the central level. LLAEPs are extracted from the EEG by means of computer based signal averaging techniques in response to repeated click stimuli. These long latency responses are picked up between 100–300 msec after giving acoustic click stimuli. Regarding generators of these waves, some have suggested fronto-central cortex to be responsible for their generation (13–15) while others have suggested the neural generators of these waves as various polysensory association areas (16). However, electrophysiological recordings in cats by implementing a series of lesions Dickerson and Buchwald have elaborated the specific neural generators for these waves in pericruciate gyrus (PCA), anterolateral gyrus (ALA) and medial suprasylvian gyrus (MSA). Some telencephalic areas might also contribute for their generation (16).

In the present study we reported LLAEPs in 4 different phases of the menstrual cycle – menstrual (1–3 days), mid-cycle (11–14 days), mid-luteal (17– 22 days) and pre-menstrual (25–27 days). So recordings were taken during periods of hormonal withdrawal, during estrogen peak, during progesterone peak and when both estrogen and progesterone are elevated. In this study effects of mainly estrogen and progesterone were seen on the most central processing of the auditory information. Results were then compared to the females taking oral contraceptives (O.C.), supposedly having no considerable endogenous hormonal fluctuations throughout the menstrual cycle.

METHODS

Twenty females of age group 19–26 years volunteered as subjects for the present study. They were instructed to chart their basal body temperature (BBT) by using '*Hanimax*' basal thermometer for 2 months prior to the study to document the ovulatory menstrual cycles. Those having irregular menstrual cycles or taking any hormonal pills were excluded from the study. Females whose menstrual cycles were not found to be ovulatory were also excluded from the study group.

Control group included 20 subjects of same age group. They all were taking hormonal contraceptive pills (0.15 mg levo-norgesterel and 30 µg ethinyl estradiol) regularly for the last 5–6 months rendering their cycles anovulatory.

Females of both the groups were given a thorough ENT checkup and those having hearing threshold of 0–20 dBHL at octave interval frequencies from 250–8000 Hz were included for the study. Long Latency Evoked potentials were recorded 4 times in a single

cycle : Menses (1–3 days), Mid-cycle (11–15 days), Mid-luteal (17–22 days) and Pre-menstrual phase (25–27 days).

Test procedure

Recordings were performed in an air conditioned, sound-proof room by using Ag/AgCl disc electrodes affixed with collodion at vertex (Cz) and left and right ear lobules (A1, A2). Grounding was done by placing an electrode on forehead. All electrodes were plugged to a junction box and skin to electrode impedance was kept below 5 Kohm. 64 alternating condensation and rarefaction click stimuli were delivered at 90 dB sound pressure monaurally through shielded headphones. Contra lateral ear was masked with a white noise of –40 dB. Signals picked up by electrodes were filtered (30 Hz and 0.5 Hz), amplified, averaged and displayed on the screen of MEB–5200 (Nihon Kohden, Japan) Evoked Potential Recorder.

Average peak latencies of positive and negative waves P1, N1, P2, and N2 were recorded for each ear separately. All the four phases were compared for each wave in both the groups and both groups were compared for each wave by using hierarchal ANOVA design. Tukey test was applied to find out the significance level within phases as well as within groups.

RESULTS

Study group : Long latency waves P2 and N2 showed a significant change in latencies during phases of menstrual cycle in normal cycling females. As shown by Table I, peak latencies of P2 and N2 components increased significantly from menses to mid-cycle, decreased during mid-luteal and again increased during pre-menstrual phase. Shortest latencies were seen during menses when body hormonal levels are smallest. P1 and N1 components also showed a similar trend but not significant results were obtained.

Control group : O.C.P. using females having anovulatory menstrual cycles were not showing such type of results. P1 and N1 components remained constant throughout the menstrual cycle although they were showing a slight rise in latencies during pill ingestion period. Long latency components P2 and N2 showed a gradual rise in

TABLE I : Showing the long latency waves in normal cycling females.

	Phase 1 (1–3 days)	*Phase 2 (11–15 days)*	*Phase 3 (17–22 days)*	*Phase 4 (25–27 days)*
	Latency (ms) (Mean ± 2SD)			
P1	70.40±5.89	73.45±9.21	71.20±8.69	71.70±6.29
N1	101.70±8.59	106.45±11.97	105.55±10.97	106.00±14.20
P2*	165.35±10.68	178.80±20.49	166.45±17.41	177.50±14.57
N2*	261.95±21.07	276.65±18.32	261.95±21.07	275.05±27.77

*P≤0.001 when P2 component is compared in all the phases.
*P≤0.001 when N2 component is compared in all the phases.

TABLE II: Showing the long latency waves in O.C. users.

	Phase 1 (1–3 days)	*Phase 2 (11–15 days)*	*Phase 3 (17–22 days)*	*Phase 4 (25–27 days)*
	Latency (ms) (Mean ± 2SD)			
P1	70.50±7.58	72.85±7.44	72.60±6.80	72.00±5.81
N1	103.35±10.21	104.60±9.66	104.50±8.68	104.52±7.69
P2*	167.65±22.21	176.45±16.28	179.85±20.64	182.65±14.46
N2*	257.35±14.60	262.60±16.21	272.45±22.60	274.80±18.69

*P≤0.002 when P2 component is compared in phase 1 and phase 3, 4.
*P≤0.001 when N2 component is compared in phase 1 and phase 3, 4.

latencies during pill ingestion period i.e., from 7–28 days (Table II).

Shortest latencies were seen during menses when no hormonal pill was being ingested.

DISCUSSION

Ovarian hormones have been found to modulate the conduction of sensory information by many researchers. Numerous tasks including visual and auditory thresholds vary systematically throughout the menstrual cycle with reduction in threshold during menstruation which implies that withdrawal of sex hormones improves hearing threshold (7, 17). Some researchers have noticed that central auditory neural pathways are more influenced by the gonadal hormones as compared to periphery (8, 9).

Long latency evoked potentials represent the most central acoustic conduction representing the waves involved in perception and discrimination of click stimuli. Possible source generators for the long latency waves N1 and P2 were found to be widely distributed over the fronto-central scalp region (13, 14). These findings have been supported by intracranial recordings from human and primate brains.

Important contribution to N1 generation derive from subcortical sources which receive projections from inferior parietal lobule such as basal ganglia, cingulate gyrus &/or amygdala (18) as N1 was preserved following frontal lobe lesions.

Studies in cats commend that polysensory association areas-peri-cruciate gyrus (PCA), anterolateral gyrus (ALA) and medial suprasylvian gyrus (MSA) contribute substantially to the generator systems of N2 and P2 waves (16). P1 do not require intact auditory or suprasylvian association cortex and appear to reflect an additional auditory processing system in parallel with the primary thalamo-cortical pathway (19).

In the present study there is a significant increase in peak latencies of P2 and N2 components during estrogen peak mid-cycle phase and decrease in latencies occurring during progesterone peak mid-luteal phase. This shows that ovarian steroids, estrogen and progesterone affect the synaptic transmission at the auditory association areas specially PCA, ALA and

MSA by modulating the secretion of GABA in a counter-regulatory fashion. Estrogen may enhance the inhibitory effects of GABA by stimulating its secretion thereby delaying the conduction. Conversely progesterone may decrease the sensitivity of neurons and blunting the estrogen potentiated GABA release. When administered alone, progesterone had no significant effect on GABA binding in any hormone sensitive brain region. Evidence to support this hypothesis emerges from several physiological and pharmacological studies of hormonal effects on auditory brainstem pathways (20).

It has been shown that estrogen and progesterone exert their effects on brain by regulating neurotransmission and membrane excitability and sex steroids interact directly with the surface membrane receptors to change the excitability of nerve cells in the hypothalamus and hippocampus (21, 22).

Estrogen has been shown to have a dual action on GABA release in female primates. Roosen Runge et al demonstrated that pulsatile release of hypothalamic GABA significantly increased in female monkeys at the time of estrogen surge and abolished during the negative feedback phase (23). This biphasic response of GABA to estrogen action helps to further explain the rise in latencies during mid-cycle in ovulating females. At mid-cycle estrogen has a positive feedback action resulting in enhanced GABA secretion in brain whereas it has a negative feedback action during early follicular and late luteal phase.

In the present study the peak latencies of P2 and N2 further increases during pre-menstrual phase. This suggests that the neuronal conduction process at the auditory association areas is relatively slower pre-menstrually. The exact mechanism responsible for such a change is not known. Retention of water and sodium due to highest levels of both estrogen and progesterone could be one of the mechanism influencing the process of axonal conduction time (24). Other mechanisms could be the progesterone withdrawal during late luteal phase, increase secretion of prolactin, aldosterone and ADH contributing to fluid retention. β-endorphin withdrawal and the direct sedative effect of prostaglandins on CNS have also been postulated to be responsible for premenstrual tension, could be causing delayed conduction (25, 26).

Females on oral contraceptives had almost similar hormonal levels throughout the menstrual cycle except menstruation. They showed a non-significant but gradual rise in latencies of P2 and N2 components during the pill ingestion period i.e., 7–28 days. This could be due to suppression of endogenous levels of gonadal steroids by the constant hormonal supply of 30 µg synthetic estrogen and 0.15 mg progestin in the contraceptive pills which inhibit LH surge. The combination O.C. therapy may manifest a somewhat similar hormonal condition as that in pre-menstrual period and fluid retention throughout their cycle may be responsible for delayed latencies during pill ingestion period.

Shortest latencies of all the waves were seen during menses in both the groups which imply that withdrawal of sex hormones improve hearing threshold.

Thus the present study provides enough electro-physiological evidence of normal

cyclic variation of sex steroids during menstrual cycle, affecting central processing of auditory sensation in the cortical association areas.

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