Gonadal steroids and auditory evoked responses during menstrual cycle

Navpreet Mann[1*], Rinku Garg[2], Yogesh Tripathi[3], Abhishek Sinha[4]

[1]Assistant Professor, [2]Professor and Head, [3]Professor, [4]Associate Professor, Dept. of Physiology, Santosh Medical College, Ghaziabad, Uttar Pradesh, India

***Corresponding Author: Navpreet Mann**
Email: drnavpreet.vmmc@gmail.com

Abstract

Introduction: Brainstem Auditory Evoked Potentials (BAEP) have been subject to effect by many physiological restrictions. The gonadal steroids may be one of them, but few electrophysiological studies have documented any evidence. This study was carried out to record the auditory evoked response in females of reproductive age group in different phases of the menstrual cycle.

Materials and Methods: This was an observational cross sectional study. The BAEP were recorded in 50 subjects (age 17-37 years, no h/o hormonal therapy) during three different phases of the same menstrual cycle. The peak latencies of the waves, I, II, III, IV and V, IPL I-III, I-V and III-V and the amplitude ratio, V/I were recorded and statistically analyzed.

Results: A statistically significant increase in the latencies of the waves, I-V in the mid cycle coinciding with high estrogen level was observed. A statistically significant decrease in the mid-luteal phase was observed which corresponds to high progesterone levels. IPL did not show any significant change in the said phases. Similarly, no significant changes in the menstrual phase was seen for all variables.

Conclusion: The results point out the BAEP changes in the mid follicular and the mid luteal phases of the menstrual cycle suggestive of effects of oestrogen and progesterone.

Keywords: Menstrual cycle, Evoked Potential, Estrogen, Progesterone.

Introduction

Female hormones pass through phases of quantitative changes during extremely important periods of life i.e. menstrual cycle, pregnancy and menopause. Pulsatile Gonadotropin Releasing Hormone (GnRH) secretion from hypothalamus at puberty initiates secretion of Follicle Stimulating Hormone (FSH) and Leutinizing Hormone (LH). FSH stimulates the growth of a few primordial follicles into Graffian follicles. Graffian follicle produces Estradiol and Inhibin. Inhibin produced by the Graffian follicle is also responsible for a fall in the FSH level and stimulation of LH secretion. The maximum estrogen secretion is seen about 48 hours before ovulation while the LH peak occurs around 24-36 hours before ovulation. LH causes the follicle to rupture at ovulation and form a Corpus luteum, which secretes progesterone. It inhibits further production of LH by anterior pituitary. In the absence of pregnancy, both estrogen and progesterone levels decline gradually. The fall in the level of these hormones brings about menstruation.[1] Correlating these hormonal changes with the 4 different phases of menstrual cycle:

Phase	Name	Days	Hormonal status
I	Menstural Phase	1 - 3	Estrogen and Progesterone withdrawl
II	Mid-cycle	11 - 14	Estrogen peak
III	Mid luteal	17 - 22	Progesterone peak
IV	Pre-menstrual	25 - 27	Both estrogen and progesterone are elevated

Brainstem Auditory Evoked Potential (BAEP) responses are a non-invasive clinical method to assess the electrophysiological events of neural excitation, conduction and transmission across the auditory pathways. BAEPs comprise of 5 or more peaks within 10ms of the stimulus. The waves of BAEP are nothing but a record of volume conducted electrical activity from auditory nerve to midbrain through medullo-ponto-leminscal system.[2]

The normal values of BAEP show variation due to age and stimulus parameters for evoking these responses. The sex differences might be due to anatomical differences in the length of auditory pathways or hormonal differences.[3] Females have a shorter latency and higher amplitude of BAEPs. The wave I-V interpeak latency is shorter by 0.1 ms in females as compared to males, which is attributed to higher core body temperature and shorter length of brainstem auditory pathway.[4]

CNS also affected by the hormonal fluctuations across the menstrual cycle. The electrophysiological characteristics of changes in sensory function during different phases of menstrual cycle have been linked to a hormonal influence.[5] Effects of estrogen and progesterone on the waves of auditory brainstem responses (ABR) have been reported. One of the various plausible explanations are retention of water and sodium affecting the availability of neurotransmitters at synapses in the auditory pathways.[6] The circulating female sex steroids affect the functioning of the sensory nervous system.[7] Other studies involving visual and auditory thresholds of click lateralization showed similar changes through the menstrual cycle with reduction in threshold during menstruation in adult women.[8] Withdrawl of Beta endorphin and prostaglandins effect on CNS may be responsible for delay in conduction.[9]

Pulsatile secretion of hypothalamic GABA is high in female monkeys at the time of estrogen surge and while touches bottom level in negative feedback phase.[10] Thus there is a biphasic response, Estrogens at mid-cycle have a

positive feedback leads to rise in GABA secretion in brain whereas a negative feedback action during follicular and late luteal phase is observed.

Different results have been reported by various authors in different studies regarding the impact of physiological fluctuations in female hormones on auditory evoked responses as assessed by different phases of menstrual cycle. The aim of this prospective study was to evaluate the effect of physiological changes in different phases of menstrual cycle on Brainstem auditory evoked responses in this part of the country.

Materials and Methods

An observational cross-sectional study was conducted in the Department of Physiology, Government Medical College, Amritsar, India. Duration of study was a complete year. A sample size of 50 female subjects of the age group 17-37 years was selected amongst the undergraduate & postgraduate students and staff of the institute. Ethical clearance was obtained from the institutional Ethics Committee. All subjects had regular menstrual cycles of 25-30 days, not taking any hormonal pills for the last 6 months and had an ideal body weight within normal range were included in the study. Written free and informed consent was taken from all the subjects prior to start the study.

During the menstrual cycle, every subject was called thrice for ABR tests, the first at the menstrual phase (day 1-3) Phase - 1, the second at mid-cycle (day 11-14) Phase - 2 and the third at mid-luteal phase (day 17-22) Phase - 3. The approximate day of ovulation was calculated retrospectively from the day of onset of next menstrual cycle. In case of any discrepancy, that cycle was exclude from the study.

Recordings were performed after explaining the details of the procedure to the subject using RMS EMG EP Mark II 2Ch (PC-based) machine. The subject lay in supine position and 4 Ag/AgCl disc electrodes were placed on the scalp. The standard protocol for application was followed. Reference - vertex (Cz) and, active - left and right ear lobes (A1, A2) and ground electrode - forehead (Fpz). First area was clean with spirit and then disc electrode placed securely with an electrode paste. Impedance was kept below 5 KOhms. For the ABR recording, first normal threshold of both the ears of every subject was recorded. Then click stimuli (2000) 60dB over and above the threshold value were given to each ear independently through shielded headphones. After filtration-amplification-averaging, the waves in the first 10ms of the latency were considered for ABR.

The peak latencies of the waves, I, II, III, IV and V, the inter peak latencies of I-V, I-III and III-V, the amplitudes of waves I and V and the amplitude ratio (V/I) were recorded. Each ear is treated as exclusive sample and waveforms were ascertained separately. This is because the pathways are separate anatomically and they can present different waveforms. However, average of the latencies was calculated because the differences were negligible. A paired data t-test was use to compare each phase of the menstrual cycle. All the recorded values were reported as mean ± SD. A p-value of <0.05 was considered to be statistically significant.

Results and Discussion

The latencies of the waves, I-V showed:

1. A statistically significant increase under the influence of high levels of estrogen in the phase- 2 subjects as compared to phase - 1. (Table 1)
2. A significant decrease under the influence of high levels of progesterone in phase-3 as compared to that in the phase- 2. (Table 2).

The IPL, amplitudes and the AR represent an inclination of increasing values in phase - 2 and decreasing in phase - 3 without a significant difference in between the phases (Tables 1 and 2).

There have been many confounding researches, which indicate that fluctuations in gonadal hormones modify auditory, olfactory and taste thresholds in an individual.[11] These can be because of effect of estrogen on the cochlea and/or auditory pathway. Impact on central processing through other pathways and alterations in blood flow in the cochlea and brain can be other mechanisms.[11] A decrease in estrogen[6] could influence the availability of neurotransmitters at the synapse and in turn, influence neural conduction time.[8] Estrogen might alter gamma-aminobutyric acid (GABA) secretion at auditory nerve synapses. Since it is an inhibitory neurotransmitter, this effect might result in delayed synaptic conduction time.[12] The relevance of estrogen mediated acetylcholine synthesis and its possible impact is also a hypothesis.[12]

Table 1 shows the comparison of absolute latencies, inter-peak latencies, amplitudes and amplitude ratio of different Waves of BAEP between proliferative phase (phase – 2) and menstrual phase (phase- 1) subjects. The absolute latencies of Waves I to V and amplitude ratio (V/I) shows a statistically significant change (increase) in proliferative phase (phase – 2) subjects compared to those in menstrual phase (phase – 1). The insignificant change in the inter-peak latencies I-III, I-V & III-V could be due to prolongation of absolute latencies of Waves I, III & V.

Table 2 shows the comparison of absolute latencies I-V, inter-peak latencies I-III, I-V & III-V, amplitudes and amplitude ratio V/I of BAEP waves between secretory (phase – 3) and proliferative phases (phase – 2). A significantly variable decrease in the absolute latencies of Waves I to V in secretory phase compared to proliferative phase is seen. Also a statistically insignificant change in IPL, amplitudes and amplitude ratio is seen. Reason for our findings can be a high progesterone content in secretory phase compared to proliferative phase. Antagonistic effect of progesterone to estrogen in phase 3 of the menstrual cycle compared to phase 2 where in there is an increase in the blood levels of estrogen only can also be a reason.

Ovarian steroids affect the synaptic transmission at the level of brainstem is obvious from the results of present study –a statistically significant increase in Waves latencies during estrogen peak mid-cycle and decrease during progesterone peak mid-luteal. The most probable reason is a

counter regulatory alteration of GABA secretion. 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 blunt the estrogen potentiated GABA release.[9]

Regulation of neurotransmission by changing membrane excitability under the effect of these hormones can be a plausible explanation as well. Interaction with the surface membrane receptors to change the excitability of nerve cells in the hypothalamus and hippocampus is known.[13,14]

A study on primates has given proofs that pulsatile release of hypothalamic GABA significantly increased in female monkeys at the time of estrogen surge and abolished during the negative feedback phase. [14] This dual behaviour of GABA to estrogen action helps to explain further the rise in latencies during mid-cycle in ovulating females. The mid-cycle estrogen rise has a positive feedback action resulting in higher GABA secretion in brain whereas it has a negative feedback action during early follicular and late luteal phase.

Table 1: Comparison of latencies, Inter-Peak intervals, amplitudes and amplitudes ratio of difference between phase-2 (Proliferative) and phase-1 (Menstrual).

Stage	Phase - 1 (Mean ± SD)	Phase - 2 (Mean ± SD)	't' value	'p' value	Significance
Latency (ms) Mean ± SD					
I	1.54 ± 0.17	1.60 ± 0.18	-2.112	0.04	S
II	2.57 ± 0.31	2.90 ± 0.14	-7.092	<0.001	HS
III	3.50 ± 0.15	3.60 ± 0.17	-3.059	0.004	S
IV	4.65 ± 0.19	4.78 ± 0.18	-3.494	0.001	S
V	5.52 ± 0.23	5.62 ± 0.22	-2.439	0.018	S
Inter-peak Latency (ms) Mean ± SD					
I-III	1.96 ± 0.25	2.00 ± 0.23	-0.916	0.364	NS
I-V	3.97 ± 0.27	4.02 ± 0.28	-0.944	0.35	NS
III-V	2.02 ± 0.25	2.02 ± 0.28	-0.108	0.914	NS
Amplitudes (μv) Mean ± SD					
I	0.63 ± 0.24	0.57 ± 0.13	1.733	0.089	NS
V	0.51 ± 0.20	0.45 ± 0.14	1.718	0.092	NS
Amplitude ratio (V/I)					
AR	1.15 ± 0.93	0.85 ± 0.36	2.413	0.020	NS

HS=highly significant (p<0.001); S=Significant (p<0.05); NS=Not significant (p>0.05)

Table 2: Comparison of latencies, inter-peak intervals, amplitudes and amplitude ratio of different waves between phase-3 (Secretory) and phase-2 (Proliferative).

Stages	Phase - 2 (Mean ± SD)	Phase - 3 (Mean ± SD)	't' value	'p' value	Significance
Latency (ms) Mean ± SD					
I	1.60 ± 0.18	1.55 ± 0.20	2.112	0.04	S
II	2.90 ± 0.14	2.61 ± 0.20	8.232	<0.001	HS
III	3.60 ± 0.17	3.53 ± 0.17	2.293	0.026	S
IV	4.78 ± 0.18	4.69 ± 0.15	3.186	0.003	S
V	5.62 ± 0.22	5.52 ± 0.25	2.237	0.03	S
Inter-peak Latency (ms) Mean ± SD					
I-III	2.00 ± 0.23	1.98 ± 0.19	0.517	0.608	NS
I-V	4.02 ± 0.28	3.97 ± 0.31	0.882	0.382	NS
III-V	2.02 ± 0.28	2.00 ± 0.28	0.44	0.662	NS
Amplitudes (μv) Mean ± SD					
I	0.57 ± 0.13	0.63 ± 0.25	-1.96	0.056	NS
V	0.45 ± 0.14	0.42 ± 0.19	1.044	0.301	NS
Amplitude ratio (V/I)					
AR	0.85 ± 0.36	0.77 ± 0.31	1.356	0.181	NS

HS=highly significant (p<0.001); S=Significant (p<0.05); NS=Not significant (p>0.05)

Conclusions and Recommendation

The present study revealed significant increase in the absolute latencies of Waves I to V and amplitude ratio V/I in the phase - 2 subjects compared to phase - 1. However the IPL I-III, I-V & III-V in the two phases did not reveal a statistically significant increase ($p>0.05$). The significant variation in absolute latencies is attributed to the high levels of estrogen hormone during the proliferative phase (phase - 2) affecting the conduction velocities. No significant change in the IPL could be due to prolongation of absolute latencies of all the Waves I, III & V.

Further comparison of secretory phase subjects to proliferative phase subjects revealed a highly significant decrease in absolute latencies of Waves I to V, and no significant change in IPL I-III, I-V and III-V and amplitude ratio V/I. It is also explained due to increased levels of estrogen in the proliferative phase enhancing the conduction velocity hence decreasing the absolute latencies and antagonistic response of progesterone to estrogen in the secretory phase subject with no effect on the latency in the secretory phase.

The present data have confirmed the existence of changes in peak latencies of Waves of BAEP during the different phases of menstrual cycle. Further studies are required to investigate, along with the blood sample collection for hormone level assessment, if the variations of wave latencies and inter-peak intervals of ABR may contribute to variation in the hearing ability of the subject, and, if so in what way.

Acknowledgment

We would like to express our sincere thanks and gratitude to the all the subjects who participated in this study.

Conflicts of interest: None.

Source of Funding: None.

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