Physical Medicine 1999; 2 (2) : 5-8

PHYSICAL MEDICINE

VEP - BAEP MODALITIES IN CHRONIC ADMINISTRATION OF SALMON CALCITONIN

SALMON KALSİTONİN KRONİK KULLANIMINDA VEP - BAEP PARAMETRELERİ

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SUMMARY

Aim of the study was to clarify whether long term using of salmon calcitonin (sCT) has any effect on stimulus processing modalities or not. BAEPs and PR-VEPs were recorded in twenty female patients with active osteoporosis aged between 46-58 and a control group age matched 20 healthy female volunteers. The mean duration of the receiving of sCT (100 İÜ / day) by the nasal way was 8±2.1 months in patient group. BAEP latencies of wave I, III and V as well as latency differences between wave I and III, and between III and V, assessed for at an intensity of 70dB above sensation level for the click did not differ among patient and control groups. PR-VEP waveform components N80, N140 and P100 were not also consistently affected in all of the subjects. Peak to peak amplitude difference between N80 and P100 were not statistically significant between groups. The results of this study did not indicate any statistically significant difference on auditory and visual evoked potentials between control group and osteoporotic women group who received sCT more than 3 months.

Key words : BAEP, VEP, calcitonin

ÖZET

Bu çalışmada salmon kalsitoninin (SCT) uzun süreli kullanımı ile uyartısal yöntem parametrelerinde etkilenim olup olmadığını araştırmak amaçlandı. 45-68 yaşlarında aktif osteoporozu olan 20 kadın hasta ile kontrol grubu olarak 20 sağlıklı gönüllü kadında BAEP ve PR-VEP' ler kaydedildi. Hasta grubunda nazal yolla sCT (100 İÜ / gün) alma süresi ortalama 8±2,1 aydı. BAEP I,III,V dalga latansları ve I-III, III ve V dalga latans farklılıklarında 70 Db üzeri uyarıda hasta ve kontrol grupları arasında fark bulunmadı. Bütün bireylerde N80, N140 ve P100 PR-VEP dalga form komponentlerinde etkilenme tutarlı değildi. N80-P100 interpik amplütüd farklılıklarında gruplar arasında istatistiksel fark bulunmadı. Bu çalışmanın sonucunda, 3 ay ve üzerinde sCT alan osteoporotik kadın ve kontrol grubu arasında işitsel ve görsel uyarı potansiyelleri arasında istatistiksel fark olmadığı gösterildi.

Anahtar sözcükler : BAEP, VEP, Kalsitonin

INTRODUCTION

Calcitonin (CT) is a polypeptide hormone secreted in the general circulation by the C-cells of the mammalian thyroid that lowers blood calcium concentration by calcium efflux from bone (1,2). However, observations suggest that CT has a broader range of actions, including effects on the central nervous system. The possible neural actions of CT include production of analgesia (3,4), changes in prolactin release (5,6), inhibition of food and water consumption (7), and other behavioral effects (8). Circulating calcitonin has shown to penetrate the blood-brain-barrier and to bind to calcitonin receptors, as well as to calcitonin gene related peptide (CGRP) receptors (9).

CGRP is a neuropeptide which arises from alternative processing of the primary RNA transcript of the gene encoding calcitonin (10). CGRP immunoreactivity has been localized in the central nervous system (11), the eye (12) and the pituitary (13). In addition release of CGRP has been demonstrated from cultured rat trigeminal ganglion cells (14). By autoradiographic analysis CGRP was found to bind to the molecular and Purkinje cell layers of the cerebellar cortex, and to the posterior substantia of the spinal cord (13). In the human brain, the highest levels of calcitonin-like peptides and binding sites have been found in the hypothalamus (11). Central administration of this peptide decreases appetite (15) and gastric acid secretion and increases sympathetic noradrenergic outflow with accompanying hypertension and tachycardia (16).

Aim of this study was to clarify whether long term using of salmon calcitonin (sCT) has any effect on stimulus processing modalities or not. Though Pietrowsky et al. (17) has shown

acute effects of sCT on visual and brainstem evoked potentials (VEP, BAEP) for healthy people, to our knowledge there is no study evaluating VEP and BAEP parameters in chronic administration of sCT in human.

MATERIALS AND METHODS

Twenty female patients with active osteoporosis aged between 46-58 and for a control group age matched 20 healthy female volunteers with no history or evidence of audilogical or any other disease were included in the study. The mean duration of the receiving of daily 100 IU sCT by the nasal way was 8 ± 2.1 months (3-36 months). Both the patients and controls had no history or evidence of occupational exposure to noise, head trauma, ototoxic damage, family history of deafness, vascular or metabolic disease. In the control group no one of the subject were taking drugs that are likely to interfere with the study and the patient group was receiving only sCT. Written consent was obtained from each patient and control subject subsequent to a thorough explanation of the purposes and the methodology that would be used in the present study. Audilogical examination prior to the evoked potential tests excluded any hearing deficiency. During testing, patients were reclined in a darkened, sound attenuated room. BAEPs and PR-VEPs were recorded and averaged on-line by a Medelec Premiere 4 (Medelec Corp. UK).

Auditory brainstem responses were obtained from the patients and controls with Ag/AgCl electrodes using two recording channels with filter bandpass between 100 and 3000Hz. Recording electrodes were attached at the vertex (reference electrode), both mastoids (active electrodes) and at a frontal location midway between nasion and the vertex (ground). Monaural rarefaction clicks (one cycle of a 3 Hz sine wave) with 0.1 msn duration were used as auditory stimuli which were delivered through earphones (TDH-39) either to the subject's right or left ear (balanced across subjects). Clicks were presented at a rate of 11,4 Hz at an intensity of 70dB above sensation level for the click. Following amplification (12 db/octave) BAEPs were averaged from series of 1000 artifact free sweeps (sweep time 10 msn; sampling rate 50 000 Hz). BAEP sweeps were excluded from analysis if the voltage of any data point exceeded 3 times of sensitivity.

PR-VEPs were recorded following checkerboard pattern reversals delivered at a stimulus rate of 1.1 Hz on a video screen. Luminance of white squares was 400cd/m2, luminance of the black squares was 4.5cd/m², resulting in a contrast of 97,5%. Pattern size was 2.3 cm thus the visual angle 1° at a distance 1.4 m between the subject's eyes and the screen. To avoid eye movements subjects had to fix their eyes on a centrally located dot on the screen. The order of stimulus conditions was balanced across subjects. PR-VEPs were amplified (filter bandpass between 1-100 Hz 12 dB/octave) and averaged from series of 100 artifact free sweeps (sweep time 250 msn; sampling rate 20 000Hz). For both of the tests interelectrode impedance was measured immediately before and after testing.

BAEP and PR-VEP waveforms were plotted in a X-Y graphy and displayed on the terminal screen to determine peak latencies and amplitudes by the use of a visual cursor. For BAEPS waves I, III and V (vertex positive), for PR-VEPs N80, P100 and N140 were determined. Measurements were made in a blind manner with respect to groups. Latency was defined as the time between stimulus onset and the maximum positive or negative amplitude. For BAEP responses also difference in latencies between wave III and I (reflecting peripheral nerve conduction velocity) and between wave V and III (reflecting central conduction velocity) were determined. Amplitudes were measured only for the N80-P100 component complex of the PR-VEP, by calculating the peak-to-peak amplitude difference between these components.

Effect of calcitonin on BAEP and PR-VEPs waves were statistically evaluated by pairwise t-tests between the groups.

RESULTS

The BAEP latencies of wave I, III and V as well as the latency differences between wave I and III, and between III and V, which were assessed at an intensity of 70dB above sensation level of the click did not differ among the patient and the control groups. PR-VEP waveform components N80, N140 and P100 were not also consistently affected in all of the subjects. Peak to peak amplitude difference between N80 and P100 were not statistical significant between groups. Results have been presented in Table I and II.

DISCUSSION

The cortical effects of auditory stimuli can be studied by a procedure called brainstem auditory evoked responses or potentials. Between 1000 and 2000 clicks delivered first to one ear

Table I: Means (±SD) of latencies (miliseconds:msn) for BAEP waves, I,III, and V for calcitonin and control groups.

	I	III	V	I-III	III-V	I-V
Calcitonin	1.73±0.3	3.75±0.5	5.94±0.46	2.07±0.16	2.18±3.09	4.2±0.33
Control	1.78±0.23	3.75±0.29	5.79±0.31	1.97±0.23	2.07±0.33	4.04±0.28

Table II: Means (±SD) of latencies (miliseconds:msn) for PR-VEP components N75, P100 and N145 (ms) for calcitonin and control groups.

	Right			Left		
	N75	**P100**	**N145**	**N75**	**P100**	**N145**
Calcitonin	69.1±11.8	101.1±7.85	145±14.7	68±7.9	100.5±7.5	143.8±14.7
Control	69.1±5	100.5±6.5	140.2±10	69±5.2	96.9±23	140.7±8.5

and then the other are recorded through scalp electrodes and maximized by computer. A series of seven waves appears at the scalp within 10 after each stimulus. On the basis of depth recordings, the study of lesions produced in cats, and pathologic studies of the brainstem in humans, it has been determined each of the first five waves is generated by the brainstem structures. The generators of waves VI and VII are uncertain. The most important parameters are the interwave latencies I-III and III-V. The presence of wave I and its absolute latency are of particular value in testing the integrity of the auditory nerve. A lesion that affects one of the relay stations or its immediate connections manifests itself by a delay in its appearence and an absence or reduction in amplitude of subsequent waves.

Pattern-shift visual evoked responses (PR-VEP) has been widely adopted as one of the most delicate tests of lesions in the visual system. Usually abnormalities in the amplitude and duration of PR-VEP accompany the abnormally prolonged latencies. PR-VEP is especially valuable in proving the existence of active or residual disease of an optic nerve.

The results of this study did not indicate any statistically significant difference on auditory and visual evoked potentials between the control group and osteoporotic women group who received sCT more than 3 months. Contrary to our findings, Pietrowsky et al. (17) have previously found some inhibitory effects of calcitonin on auditory and visual sensory processing. Specifically, their findings included a minimally longer latency for waveform V in 40 Hz and 60 Hz but not in 80 Hz. among BAEP waveforms. Additionally, among VEP parameters, a statistically significant difference was found with 0.1 IU/kg sCT but not with 1 IU/kg sCT on N80 waveform. There were no significant differences among any other BAEP waveforms and other VEP potentials such as P100 and N140. Based on these results, Pietrowsky et al. (17) proposed a mutual relationship between somatosensory inhibition and pain controlling activities of calcitonin. Our study did not support this assumption; none of the BAEP and VEP parameters were statistically different between groups. Several speculations may be done to explain the inconsistency of the results between our and their studies. Their study include 12 subjects and non-parametric statistics were used for analysis. Moreover, if inhibitory effects are responsible from pain controlling effects of CT, one would expect to see higher effects with higher doses of sCT on VEP potantials. This is not the case in their study. Although some effects observed in N80 with lower dose, no statistically significant effects noted with higher doses. Based on these shortcomings, it is possible to conclude that, unless supported with other studies, the results of Pietrowsky's study are highly speculative and inconclusive. Longer term effects of sCT may also be different than acute administration and may explain the differences between studies.

Input to the ventrolateral segment of the periaquaeductal gray matter (PAG) predominantly originates from lateral hypothalamus, preoptic area and lateral habenula (18). If the receptors in the PAG represent target sites for CT-containing neurons, it is very likely that their cell bodies would also be located in these hypothalamic and limbic structures. Alternatively, these receptors may be targets for intrinsic CT neurons (19). The PAG also seems to be one of the sites of action of opiates in inducing analgesia. While both opiates and CT share a common focus in producing analgesia, there are important differences between two classes of compounds. The finding that CT injected into the PAG and hindbrain structures has analgesic properties and that receptors are localized at the sites of injection indicates that these regions are important sites of ac-

tion of CT in eliciting analgesia. The fact that in this central action as in others, sCT is much more potent than human CT raises the question of whether all of these central effects are related to the 32-amino acid 'classic' thyroidal CT peptide or to an unknown endogenous sCT-like peptide (19). It is shown that CGRP that is synthesized by motor neurons, increases the number of Acetylcholine receptors on the muscle surface, apparently by activating cAMP within the muscle cell (20). Unfortunately this is the unique finding about the effects of the calcitonin or CGRP on pre- or postsynaptic receptor sites. Though characteristic and anatomically distinct pattern of distribution suggests multiple roles for the peptide including modulation of auditory, visual, gustatory and somatosensory processing and neuroendocrine control, today we can only speculate the details of the mode of action of these peptides.

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