Effects of Salmon Calcitonin on Somatosensory Evoked Potentials

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Abstract. Besides its Ca^{++} regulative effects, calcitonin is known to diminish sensitivity to painful stimuli. The present study aims to clarify whether calcitonin has similar effects on stimulus processing in other modalities. The study was performed according to a double-blind and placebo controlled protocol. Sixteen patients with osteoporosis were given intramuscularly 100 IU salmon calcitonin (sCT) or 1 ml saline solution as placebo, randomly on first and fifteenth days. One hour after injection, SEP's were recorded at the scalp, following right posterior tibial nerve stimulations at the ankle. Latencies of wave-form modalities and amplitude did not differ between sCT and placebo groups ($p > 0.05$). However, latency differences of N42-N65 (ΔLAT) and area were significantly prolonged in sCT group ($p < 0.05$). As a result we can speculate that sCT can change some SEP modalities which can be interpreted as the central effects of sCT.
Key words: Calcitonin, Analgesia, SEP.

INTRODUCTION

Calcitonin (CT) is a polypeptide hormone with 32 amino-acid residues secreted in the general circulation by the C-cells of the mammalian thyroid that lowers blood calcium concentration by inhibiting 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, 8], and other behavioral effects[9].

Circulating calcitonin has been shown to penetrate the blood-brain-barrier[10] and to bind to calcitonin receptors, as well as calcitonin gene related peptide (CGRP) receptors[11]. Both CT and CGRP have reduced the nociceptive response[12].

The dorsomedial nucleus of the hypothalamus, the preoptic area and the centromedial nucleus of the thalamus are sensitive to sCT injection[13].

Effects of calcitonin on painful stimuli are well established in animals and humans[14, 15]. In these studies, calcitonin has been consistently found to reduce sensitivity to painful stimuli. Intra-ventricular (ICV) injection of eel-calcitonin showed analgesic activity in rats as evaluated by the "hot-plate test". In patients suffering from bone metastases, IM injection of 100 IU/day salmon-calcitonin resulted in a significant relief from bone pain compared to placebo treatment. Also in osteoporosis, calcitonin exerts an analgesic effect that is unrelated to its effect on bone but the precise mechanism has yet to be clarified[16]. The treatment with analgesic doses of salmon-calcitonin enhances the in vitro effects of kappa- and delta-opioid agonists. The increase of the effectiveness

of the opioid agonists may be one of the mechanisms involved on the analgesia induced by salmon-calcitonin[17].

In this context, the question arises, whether the antinociceptive action of sCT reflects a more general influence of sCT on sensory processing. The present study aims to clarify whether calcitonin has effects on somatosensory evoked potentials.

MATERIALS AND METHODS

Sixteen women with osteoporosis, aged 50–68 (59.1 ± 4.7) years, were enrolled in this study. They were not under current medication, and had had to abstain from coffee and alcoholic beverages for 12 hr prior to the recordings. Written consent was obtained from each patient subsequent to a thorough explanation of the purposes and the methodology to be used in the present study.

The study was held double-blind and designed according to a within subject-crossover comparison, i.e., each subject was tested during two sessions, after having received saline solution as placebo and 100IU sCT. Treatments were applied intramuscularly 60 min before recording.

SEP's were recorded and averaged on-line by a Medelec Premiere 4 (Medelec Corp. UK). The right posterior tibial nerve at the ankle was stimulated with a bipolar surface stimulating electrode. Before induction the stimulus intensity was equal to the algebraic sum of the sensory and motor thresholds. This intensity produced a distinct toe twitch. Display sensitivity was 10 μV and the response reject level was 5 times sensitivity. The recording subdermal needle electrodes were placed at the scalp at FPz (reference) and C3' of the international 10–20 system for scalp electrode placement. The wraparound patient ground electrode was wrapped around the wrist. Electrode impedance was maintained at less than 3 kohm and interelectrode impedances were measured immediately before and after testing. Two hundred and fifty-six constant current stimuli of 100 μs duration were delivered at a rate of 5 Hz. Input filtering was set to a band width of 10 Hz–2 kHz for scalp recordings, and a time base of 100 ms following the stimulus was analyzed.

SEP's waveforms were X-Y plotted and displayed on the terminal screen. Peak latencies and amplitudes of N42, P50, N65 waves were determined by the use of a visual cursor. Measurements were made in a blind manner with respect to patient's therapy. Latency (ms) was defined as the time between stimulus onset and the maximum positive or negative amplitude and difference of latencies between N42–N65 (ΔLAT) were determined. Amplitudes (μV) were measured only for the N42–P50 component complex of the SEP, by calculating the peak-to-peak amplitude difference between these components. The area of the negative component (nVs) was calculated automatically by the machine.

The results were statistically evaluated by the Levene test for variance homogeneity and t-tests for independent samples between the groups.

RESULTS

Results indicated that sCT compared with placebo increased the difference between peak latencies (ΔLat) ($P<0.05$) and negative waveforms' area ($P<0.05$). Mean latencies of waves N42, P50 and N65 did not differ between sCT and placebo groups and although the latencies of P50 and N65 appeared to be prolonged with sCT, the results were not statistically significant. The peak to peak amplitude difference (N42–P50) was also not sta-

Table 1. Means (± SD) of latencies and amplitudes for SEP components in calcitonin and control groups

	SCT Group	Placebo Group	P Value
Latency of N42 (ms)	44.6 ± 3.1	45.1 ± 2.8	P>0.05
Latency of P50 (ms)	54.8 ± 3.8	53.2 ± 3.4	P>0.05
Latency of N65 (ms)	66.9 ± 4.3	64.3 ± 4.6	P>0.05
Lat (ms)	22.2 ± 3.3	19.1 ± 3.6	P<0.05*
Amplitude (mV)	2.8 ± 1.7	1.8 ± 1.0	P>0.05
Area (nVs)	87.1 ± 43.5	59.8 ± 40.6	P<0.05*

*statistically significant.

tistically significant between groups (p>0.05). The results are summarized in Table 1.

DISCUSSION

Our results demonstrated that sCT 100 IU by the IM route compared with placebo did not change any latency value of SEP waveform modalities, and it can be speculated that sCT does not effect peripheral pain conducting pathways. This finding is consistent with the other studies indicating the effects of analgesic drugs on SEP parameters. It has been shown that aspirin, paracetamol and codeine do not change SEP latencies or amplitudes[18].

Besides the above findings, somatosensory evoked responses (SEP) have been found to be enhanced following induction of anaesthesia with ketamine. However, the increases in amplitude were small compared with SEP-enhancing effects of etomidate. The increase in somatosensory evoked responses may reflect dose-dependent disinhibition and/or increased excitation of cerebral neuronal activity induced by ketamine or etomidate. Attenuation of late cortical somatosensory evoked responses following stimulation of thin C- and A delta-nerve fibres has been reported in volunteers given low-dose ketamine. The changes in SEP amplitude correlated with the changes in subjective pain sensation. Consequently, it was concluded that the analgesic effect of ketamine can be assessed by electrophysiological measurement methods. Recent studies suggest that the analgesic effect of the racematic ketamine mixture can probably be related to the effects of S-(+)-ketamine isomer, which has been shown to be involved in the activation of an opioidergic mechanism[19]. The foregoing results on analgesic efficacy have been ascribed to calcitonins, presumably due to a direct hormonal effect on calcitonin receptors in the brain[13, 20] and interactions between calcitonin and the opioid system. The treatment with analgesic doses of salmon-calcitonin enhances the in vitro effects of kappa- and delta-opioid agonists. The increase of the effectiveness of the opioid agonists may be one of the mechanisms involved on the analgesia induced by salmon-calcitonin[17, 21].

In this study we found that sCT increased the difference of latencies between N42–N65 (ΔLAT). This finding indicates that sCT lengthens signal processing time in the brain and it can be interpreted as an indicator of disinhibition and/or increased excitation of cerebral neuronal activity. The area under the negative component was also significantly greater than in the placebo group in our study. Jasper reported that the area under the curve which was recorded in electroneurographic studies provided the most direct estimate of the amount of functioning tissue that was generating the waveform[22]. It can be speculated that this can be another indicator of a central signal processing effect of sCT and it is consistent with Pietrowsky's results who demonstrated an inhibitory influence of calcitonin on auditory and visual sensory processing[23].

As a result we can speculate that sCT can change some SEP modalities which can be interpreted as the central effects of sCT and these modified parameters might be due to the disinhibition and/or increased excitation of cerebral neuronal activity.

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