Human Midbrain Auditory Evoked Potentials Do Not Differ Between Bursts and Suppressions of Cortex Activity in Propofol Anesthesia: Case Report

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Case Report

Abstract

Propofol, the most widely administered anesthetic agent, is used for sedation and general anesthesia. During general anesthesia it can induce bursts and suppressions of cortex activity, which exact mechanism of generation has not been identified yet. The aim of study was to investigate the difference between midbrain auditory evoked potentials recorded during bursts and suppressions of cortex activity. These potentials were registered from the drainage-electrode implanted in the cerebral aqueduct of an adult patient with an obstructive hydrocephalus who had undergone pineal region tumor removal through anterior interhemispheric translaclosal approach. The cortex activity was divided into rare bursts of alpha activity (total length of 9 seconds) and prolonged suppressions (total length of 104 seconds). Midbrain auditory evoked potentials included long latency peaks with no statistically significant difference in their amplitudes and latencies between bursts and suppressions of cortex activity. The results suggest that human midbrain auditory evoked potentials do not differ between bursts and suppressions of cortex activity in propofol anesthesia. Therefore, for clear midbrain auditory evoked potentials cognitive but not the total electrical activity of the cortex should be suppressed.

Keywords: human midbrain, deep electrodes, propofol, auditory evoked potentials.

Introduction

Propofol, the most widely administered anesthetic agent, is used for sedation and general anesthesia. It binds post-synaptically to gamma-aminobutyric acid (GABA) type a receptors where it induces an inward chloride current, which hyperpolarizes the post-synaptic neurons thus leading to inhibition [1,2]. In the cortex, propofol induces GABA-mediated inhibition of pyramidal neurons and the thalamic reticular nucleus, a network that provides important control of thalamic output to the cortex [3,11]. Propofol also decrease activity of midbrain arousal centers: pedunculopontine tegmental nucleus, lateral dorsal tegmental nucleus, the locus coeruleus, the dorsal raphe nucleus and ventral periaqueductal grey substance [4]. Consequently, dorsal raphe nucleus activates the cerebral cortex, thalamus, hippocampus, amygdala, cerebellum and numerous brainstem nuclei less in propofol anesthesia [5]. Locus coeruleus does not affect the cortical mantle in propofol anesthesia [6,7]. Laterodorsal tegmental and pedunculopontine tegmental nuclei reduce their stimulating effect on the thalamus and basal forebrain regions such as the substantia innominata in propofol anesthesia [8,9,10]. Therefore, decreasing excitatory inputs from the thalamus and the brainstem to the cortex enhances hyperpolarization of cortical pyramidal neurons, consequently, propofol-induced loss of consciousness (PLC) occurs [11].

When dose of propofol is high, it can induces periodical bursts (BCA) and suppressions (SCA) of cortex activity [11,12]. The exact mechanism of their generation has not been identified yet [13]. In our previous study, we found long latency components (N60, P80, N120 and P150 peaks) of midbrain auditory evoked potentials (mAEP) in anesthesia (without splitting the record into BCA and SCA) and recovery after anesthesia [14]. These components were clearly identified in anesthesia but they were illegible and noisy in recovery after anesthesia.

The present study is aimed to investigate the difference between mAEP recorded during BCA and SCA in order to evaluate the influence of cortex activity on midbrain in mAEP and the involvement of midbrain in BCA and SCA generation.
Materials and Methods

The study included one male patient of 37 years old with tumor of the pineal region with obstructive hydrocephalus who underwent tumor removal through anterior interhemispheric transealosal approach. After removal of the tumor at the final stage of the operation, a specially developed external ventricular drainage was installed for 24 hours for the purpose of draining cerebrospinal fluid (CSF) and preventing CSF discirculation. Three ring electrodes (the two distal electrodes were recording and the proximal one was indifferent) 3 mm long were attached to the distal end of the drainage 3 mm (between recording electrodes) and 10 mm (between the deepest recording electrode and referent electrode) apart. More information about the operation technique and experiment presentation is available in the studies [14,15].

Patient was without cognitive disorders before operation. Simultaneous recording of scalp and midbrain potentials was performed in propofol anesthesia (6 mg/kg/hour) with oddball paradigm in passive conditions. The dose was calculated by the anesthesiologist taking into account the characteristics of the patient and the course of surgery. Cortex potentials were recorded from 19 scalp electrodes located by the 10-20% system using ear indifferent electrodes with quantization frequency of 500 Hz. Experimental blocks of a 100 stimuli (80% - 800 Hz 90 ms, 76 dB; 20% - 600 Hz 90 ms, 76 dB) were performed with Presentation software. Only frequent tone of 800 Hz was included in this study: 10 responses, which occurred during BCA, and 10 responses during SCA. The number of responses analyzed was reduced for BCA since only 10 frequent tones of 800 Hz occurred to be performed in periods of BCA. Accordingly, 10 random responses were taken from periods of SCA for equal comparison with BCA.

Brain potentials were analyzed with MATLAB (R2015b, Math Works, USA) Brainstorm toolbox. Band-pass filter (0,5-49 Hz) and heartbreaks removal via signal-space projection approach were applied to the record to exclude artifacts. Quality of recording sites containing auditory stimuli was visually evaluated. Artifact sections were excluded from the study. The time domain of mAEPI contained 100 ms of a pre-stimulus signal (baseline) and 200 ms of a post-stimulus signal. Statistical analysis was performed with STATISTIKA10 software. Mann-Whitney U test was calculated for the difference of amplitudes between N60 and P80 and between N120 and N150 peaks of not averaged mAEPI and for latencies of these peaks of averaged mAEPI.

The recording sections with amplitude more than 2 uV were considered as BCA, the rest were considered as SCA (figure 1 B). The amplitude-frequency Morlet wavelet analysis across the whole record was carried out from O2 scalp site (the site with highest amplitude of BCA) to estimate the BCA frequency composition (figure 1 A). Burst suppression ratio (a number between 0 and 1 which measures the fraction of time in a given time interval that the electroencephalogram is suppressed) was also counted [16].

Results and Discussion

During recording in anesthesia, the electroencephalogram (EEG) of the patient unexpectedly divided into rare BCA (total length of 9 seconds) and prolonged SCA (total length of 104 seconds). BCA mainly consisted of rhythmic alpha activity of 11-13 Hz with the largest amplitude in O1, O2, P3, P4, PZ and T6 sites (Figure 1, A). SCA covered larger part of the recording (Figure 1, B). Burst suppression ratio was approximately 0,92.

Figure 1: A - Wavelet analysis of the whole record from O2 scalp site. B - The whole EEG from the midbrain (D1 and D2) and FZ, CZ, P3, P4, O1, O2 scalp sites. Red lines between figures 1 A and 1 B mark BCA areas of the record.

There were no clearly detected peaks on scalp evoked potentials (Figure 2 A, B). N60, P80, N120 and P150 peaks were visible on mAEPI from both deep electrodes during SCA and BCA (Figure 2 A, B, Table 1). Mann-Whitney U-test for mAEPI from D1 and D2 electrodes showed no significant difference in amplitudes and latencies of these peaks between SCA and BCA (p>0,05).
Figure 2: Auditory evoked potentials from midbrain (red lines) and scalp (grey lines) electrodes. A - 10 averaged responses, which occurred during SCA. B - 10 averaged responses, which occurred during BCA.

### Table 1: Characteristic of mAEP in propofol anesthesia

| Midbrain electrode | mAEP peak | BCA latency, ms | Δ of A*, uV | SCA latency, ms | Δ of A*, uV |
|--------------------|-----------|-----------------|-------------|----------------|-------------|
| D1                 | N60       | 64              | 0.6         | 64             | 0.8         |
|                    | P80       | 80              |             | 82             |             |
|                    | N120      | 144             | 2.7         | 142            | 2.22        |
|                    | P150      | 162             |             | 162            |             |
| D2                 | N60       | 64              | 0.73        | 64             | 1.03        |
|                    | P80       | 80              |             | 84             |             |
|                    | N120      | 144             | 2.83        | 142            | 2.25        |
|                    | P150      | 162             |             | 162            |             |

*Δ - difference of amplitudes between two peaks*

The absence of N100 and N200 peaks on scalp evoked potentials in response to frequent tone indicates lack of cognitive processes \[17\].

The burst suppression ratio is used as one of the markers of PLC \[18\]. BCA are usually consist of frontal alpha waves, which also indicate PLC. In that case, normal communications are supposed to be interrupted between the thalamus and frontal cortex or between parietal and frontal cortex \[1\]. In the current research, alpha waves had the largest amplitude in occipital and parietal sites that is more common for eyes-closed resting state \[19\]. Such a displacement of the peak of alpha activity may appear because of previous brain damage due to tumor. Nevertheless, BCA activity could influence the mAEP only via general excitement or conductivity of brain tissue. The influence of conductivity was eliminated by deep located referent electrode. In the case of general brain excitement, mAEP would have to be different between BCA and SCA. The finding suppose that BCA do not affect the midbrain neurons potentials.

On the other hand, there is an evidence of the involvement of midbrain structures (dorsal raphé nucleus and others) in PLC \[4\]. Their participation in generation of BCA or SCA should have reflected on mAEP because of a large number of connections within midbrain and small amount of nerve tissue in the midbrain that facilitates electrical conductivity \[6\]. Results of the current study suppose no involvement of human midbrain in generation of BCA and SCA.

Since human mAEP do not differ between BCA and SCA in propofol anesthesia, cognitive but not the total electrical activity of the cortex should be suppressed for registration of clear mAEP.

This study also had some limitations. There was no possibility to check the results in healthy subjects. So in this case report we investigated individual data instead of comparing with the control group. The computer tomography scan resolution does not allow us to determine the exact positions of the deep electrodes relative to the structures of the midbrain. We can only claim that recorded deep electrodes were in the aqueductus cerebry near the border with the fourth ventricle. The total duration of records in anesthesia did not exceeded 10 minutes. This allows us to assume that the EEG in the state of deep anesthesia was recorded in the steady state of the brain. Contribution of consciousness recovery in the obtained data was not significant. Low percent of BCA did not allow us to use other kinds of auditory stimuli, which were presented to the patient during the record \[14\].

### Conclusions

The data obtained suppose that human mAEP do not differ between BCA and SCA in propofol anesthesia.

### ethics approval and consent to participate

Ethical approval of the research methods was obtained from N.N. Burdenko National Medical Research Center of Neurosurgery Ethics Committee (protocol №1/2016).

### List of abbreviations

- Burst of cortex activity (BCA)
- Cerebrospinal fluid (CSF)
- Electroencephalogram (EEG)
- Gamma-aminobutyric acid (GABA)
Midbrain auditory evoked potentials (mAEP)
Propofol-induced loss of consciousness (PLC)
Suppressions of cortex activity (SCA)

Data Availability

The data underlying the findings of the study is stored in N.N. Burdenko National Medical Research Center of Neurosurgery. Readers can request access to the data via corresponding author.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Authors’ contributions

Project authorship, idea presentation and neurosurgical operation: DP; conceived and designed the experiment: DP, LO, VP, MK; performed the experiment: DP, LO, VP, MK, OZ; analyzed the data: AK, LO, EM, VP; wrote the paper: AK, LO, EM, VP, DP.

References

[1] Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical Electroencephalography for Anesthesiologists. Anesthesiology 123(4) (2015): 937–960.
[2] Hemmings HC, Jr, Akabas MH, Goldstein PA et al. Emerging molecular mechanisms of general anesthetic action. Trends Pharmacol Sci. 26 (2005): 503–10.
[3] Bai D, Pennefather PS, MacDonald JF, Orser BA. The general anesthetic propofol slows deactivation and desensitization of GABA (A) receptors. J Neurosci 19 (1999):10635–46.
[4] Brown EN, Purdon PL, Van Dort CJ. General Anesthesia and Altered States of Arousal: A Systems Neuroscience Analysis. Annual Review of Neuroscience 34(1) (2011): 601–628.
[5] Vasudeva RK, Lin RCS, Simpson KL, Waterhouse BD. Functional organization of the dorsal raphe efferent system with special consideration of nitergic cell groups. Journal of Chemical Neuroanatomy 41(4) (2011): 281–293.
[6] Parvizi J, Damasio A. Consciousness and the brainstem. Cognition. 79(1-2) (2001):135-60.
[7] Moore RY, Bloom FE. Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. Annual Review of Neuroscience 2 (1979): 113-168.
[8] Pare D, Smith Y, Parent A, Steriade M. Projections of brainstem core cholinergic and noncholinergic neurons of cat to intralaminar and reticular thalamic nuclei. Neuroscience 25 (1) (1988): 69-86.
[9] Steriade M. Central core modulation of spontaneous oscillations and sensory transmission in thalamocortical systems. Current Opinion in Neurobiology 3 (4) (1993): 619-625.
[10] Muller CM, Lewandowski MH, Singer W. Structures mediating cholinergic reticular facilitation of cortical responses in the cat: effects of lesions in immunocytochemically characterized projections. Experimental Brain Research 96 (1) (1993): 8-18.
[11] Amzica F. Basic physiology of burst-suppression. Epilepsia (2009): 50 (Suppl 12):38–9.
[12] Ching S, Purdon PL, Vijayan S, Kopell NJ, Brown EN. A neurophysiological-metabolic model for burst suppression. Proc Natl Acad Sci U S A 10 (2012):3095–100.
[13] Kenny JD, Westover MB, Ching S, Brown EN, Solt K. Propofol and sevoflurane induce distinct burst suppression patterns in rats. Frontiers in Systems Neuroscience (2014): vol. 8, no. 237.
[14] Kantserova AO, Oknina LB, Masherov EL, Podlepih VV, Zaitsev OS and Pitskhelauri DI. Human midbrain participates in mismatch detection without cognitive activity of the cerebral cortex: case report. Archives of Clinical and Biomedical research. 2019; 3: 296-314.
[15] Oknina LB, Kantserova AO, Masherov EL, Podlepih VV, Zaitsev OS, Pitskhelauri DI. Functional connectivity between the midbrain and cortex during consciousness recovery after general anesthesia. Wjpmr 5(2) (2019): 237-249.
[16] Rampil JI, Weiskopf RB, Brown JG et al. Isoflurane produce similar dose-related changes in the electroencephalogram of pigs. Anesthesiology 69 (1988): 298–302.
[17] Naatanen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 24 (1987): 375–425.
[18] Bruhn J, Bouillon TW, Shafer SL. Bispectral index (BIS) and burst suppression: revealing a part of the BIS algorithm. Journal of clinical monitoring and computing. 2000; 16:593–6.
[19] Lopes Da Silva FH, Storm Van Leeuwen W. The cortical source of the alpha rhythm. Neuroscience Letters 6(2-3) (1977): 237–241.