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Effect of ethanol on the visual-evoked potential in rat: dynamics of ON and OFF responses

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The effect of acute ethanol administration on the flash visual-evoked potential (VEP) was investigated in numerous studies. However, it is still unclear which brain structures are responsible for the differences observed in stimulus onset (ON) and offset (OFF) responses and how these responses are modulated by ethanol. The aim of our study was to investigate the pattern of ON and OFF responses in the visual system, measured as amplitude and latency of each VEP component following acute administration of ethanol. VEPs were recorded at the onset and offset of a 500 ms visual stimulus in anesthetized male Wistar rats. The effect of alcohol on VEP latency and amplitude was measured for one hour after injection of 2 g/kg ethanol dose. Three VEP components – N_{63}, P_{89} and N_{143} – were analyzed. Our results showed that, except for component N_{143}, ethanol increased the latency of both ON and OFF responses in a similar manner. The latency of N_{143} during OFF response was not affected by ethanol but its amplitude was reduced. Our study demonstrated that the activation of the visual system during the ON response to a 500 ms visual stimulus is qualitatively different from that during the OFF response. Ethanol interfered with processing of the stimulus duration at the level of the visual cortex and reduced the activation of cortical regions.

Key words: ethanol, visual-evoked potentials, visual cortex, ON responses, OFF responses, rat

One of the fundamental characteristics of sensory stimulus is its duration. Stimulus ON and OFF responses are used to measure stimulus duration. Previous studies have shown that ON and OFF responses may vary across sensory systems and stimulus processing phases (Noda et al. 1998, Yamashiro et al. 2008). Research on the sensory systems revealed that different components of evoked ON and OFF response depend on stimulus duration and interstimulus interval (Hari et al. 1987, Noda et al. 1998, Spackman et al. 2006, Yamashiro et al. 2008, 2009). In order to record fully separated ON and OFF responses, the stimulus duration should be 500 ms or greater (Hari et al. 1987, Spackman et al. 2006). This phenomenon has been observed in different sensory systems: somatosensory, auditory and visual.

Studies of the visual system showed that visual stimulus ON and OFF responses were affected not only by stimulus duration but also by its contrast (Wilson and Mitchell 1983). Single cell studies demonstrated that cells of the visual system were taking longer to turn on (i.e., to increase the firing rate) than to turn off and that the onset latency was more varied and depended on the stimulus characteristics as compared to the offset latency (Bair et al. 2002). This phenomenon has been observed in the lateral geniculate body and the visual cortex, and did not depend on cell class or stimulus type (Bair et al. 2002). These findings suggest that the event offset provides more reliable timing cues to the visual system than the event onset. Recent findings in the visual system of drosophila revealed that even in flies, which have very simple neural circuitry, there is a neuronal selectivity for light-on and light-off in the layers of the medulla, associated with two anatomically derived pathways (Strother et al. 2014). This implies that processing of stimulus onset and offset should be based on different circuitries and, correspondingly, different neuronal mechanisms in organisms with a more complex nervous system, e.g. rodents.

Responses of sensory systems are modulated not only by various parameters of the stimuli, but also by the state of the organism, which in turn can be modulated by various biologically active substances. Ethanol is one of the most widely used substances in the world that alters the functioning of the central nervous system (CNS). The effect of ethanol on the CNS is typically manifested by altered visual perception, which is caused by incorrect processing of sensory information. It has been shown that ethanol affects spatial frequency discrimination (Watten et al. 1998), contrast discrimination (Pearson and Timney 1999) and processing (Zhuang et al. 2012), depth perception (Hill and Toffolon 1990), visual acuity (Wilson

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and Mitchell 1983), reduction or elimination of lateral inhibition in retina (Johnston and Timney 2008) and properties of single cell receptive field (Chen et al. 2010). Functional changes in the processing of the stimulus onset and offset were shown to be associated with the reaction-time to the sensory input (Hari et al. 1987, Serviere et al. 1977, Yamashiro et al. 2008, Yamashiro et al. 2009). Incorrect processing of visual stimuli onset and offset may change the reaction-time (Jensen 1990, Nicolas 1997, Posner 2005), which in turn can significantly increase the likelihood of alcohol-induced accidents.

One of the best methods to investigate temporal resolution of the sensory processing is to record visual evoked potentials (VEP) – responses to light flash (up to 5 ms). Individual VEP components reflect different stages of visual stimulus processing (Hetzler and Bauer 2013). In the rat, VEP component N_{63} reflects intracortical or subcortical (but not direct dLGN) input to the VC, P_{89} results from connections between the superior colliculus, brainstem and diffuse thalamic projections (Creel et al. 1974) and N_{143} represents secondary activation of cortical pyramidal cells (Meeren et al. 1998). The effect of acute ethanol administration on flash evoked potentials (FEPs) was investigated in numerous studies. Begleiter and others (1972) demonstrated that the effect of ethanol was stronger on the visual cortex than on the reticular formation. It has been shown that cortical structures were more susceptible to the depressant effect of ethanol than subcortical structures (Begleiter and Coltrera 1975). Further studies have shown that amplitude and latency of individual components responded differently to acute ethanol application (Hetzler and Bauer 2013, Hetzler and Bednarek 2001, Hetzler and Martin 2006, Hetzler and Ondracek 2007, Hetzler et al. 1981, Hetzler et al. 2008).

Despite numerous data on responses to stimulus onset and offset, as well as the effect of ethanol on different levels of the visual system, it is still unclear: 1) which brain structures are responsible for the differences observed in the processing of ON and OFF response; 2) whether ethanol affects the different stages of information processing during stimulus onset and offset equally. To answer these questions we recorded VEP responses to stimulus onset and offset following application of ethanol and analyzed latency and amplitude of different VEP components.

For the experiments ten two-month-old male Wistar rats (from our own breeding colony at the Vilnius University, Vilnius, Lithuania) were used. All animals were housed individually in standard rat cages under a 12/12-hour artificial light/dark cycle (lights on at 7:00 a.m.). Room temperature was kept constant (temperature: 22±1°C). Standard laboratory rat food (4RF21-GLP, Mucedola srl, Milan, Italy) and tap water were provided *ad libitum* throughout the experimental period. Body weights were measured weekly. All experimental procedures were approved by the State Food and Veterinary Service of the Republic of Lithuania.

Rats were anesthetised with 5% sevoflurane and maintained anesthetised with 3% sevoflurane during the entire surgery. The recording electrode (0–80×1/8 inch stainless steel screw) was placed above the visual cortex (coordinates AP: –7 mm; ML: ±3 mm). The grounding and the reference electrodes were placed above frontal cortex (coordinates AP: +2 mm, ML: ±2 mm). Dental cement (Prevest DenPro, Jammu, India) was used to ensure stability of electrodes and protection from the environment. During the whole surgery animal temperature was maintained at 37°C by using a temperature controller (ATC1000, WPI, Sarasota, USA). After the surgery rats were given daily Carprofen injection (SC) for pain relief (4 mg/kg, Rycarfa, KRKA, Novo mesto, Slovenia) for three days and antibiotics, Enrofloxacin (5 mg/kg, Vetoquinol Biowet, Gorzow Wielkopolski, Poland), for seven days (Lee-Parritz 2007). Rats were allowed to recover for two weeks before recordings of visually evoked potentials began.

All recordings were done in sevoflurane anesthetized animals. VEPs were recorded for one hour under three different conditions: baseline, following intraperitoneal (IP) administration of 0.9% saline and 2 g/kg of ethanol. The order of experiments was randomized. Recording of evoked potentials started 2 min after saline/ethanol injections.

For VEP recordings stimuli were presented via an LCD monitor (SyncMaster P22370, Samsung); refresh time was 2 ms and the distance to the eye was 20 cm (monitor light covered all visual field). In order to protect rat eyes from drying, they were covered with transparent Lacripos (Ursapharm, Saarbrucken, Germany) gel (Geiger et al. 2008, Mostany and Portera-Cailliau 2008). Visual stimulation was performed with the software VisStim 1.0. with 500 ms stimulus duration, 125 cd/m^2 intensity, 1 lx background illuminance and 0.25 Hz stimulation frequency was used. The VEP recordings started 100 ms before the application of stimulus and continued for 2900 ms after the stimulus onset. Stimuli were presented with an interval of 3.5 s. The one hour recording interval was divided into nine time windows of 400 s. In each time-window a visual stimulus was presented 100 times. Average VEPs calculated from 100 responses during each time window were used for data analysis.

Data collection was made with data acquisition system (Power 1401, CED, UK) using 1 kHz sampling rate. Evoked potentials were amplified (gain ×1000) with a standard biopotential amplifier (Iso-DAM8A, WPI) using high (1 kHz), low (1 Hz) and notch (50 Hz) built in filters. Data analysis was performed using Signal 5.07 (CED, UK) software.

VEP components were marked by their polarity (the positive peaks are noted P and the negative – N) and by their latency from the onset and the offset of the stimulus. The amplitude of component N_{63} was measured using the baseline-to-peak method, amplitude of other components – using the peak-to-peak method. The baseline-to-peak amplitude was calculated as the difference between mean voltage of 100 ms before stimulus onset/offset and the peak voltage. The peak-to-peak amplitude was calculated as the difference between two peak voltages (e.g. amplitude of component P_{89} is voltage difference between P_{89} and N_{63} peaks, Fig. 1A). Peak latencies were calculated relative to stimulus onset (i.e., 0 ms) and offset (i.e., 500 ms), see Fig. 1A.

VEP recordings under baseline condition did not differ from recordings following saline administration (for all components $P>0.05$). Therefore, the effect of ethanol administration on latency and amplitude of VEP was assessed by comparing it with recordings after saline administration. Two-way repeated measures ANOVA was used for analysis of VEP amplitude and latency of three the most common peaks – N_{63}, P_{89} and N_{143} [factors: time and treatment]. Differences between latencies of ON and OFF responses for components N_{63}, P_{89} and N_{143} under different treatment conditions were analysed using two-way repeated measures ANOVA [factors: time and stimulus type (ON *vs.* OFF)]. Whenever significant differences were found, a *post hoc* Student Newman-Keuls

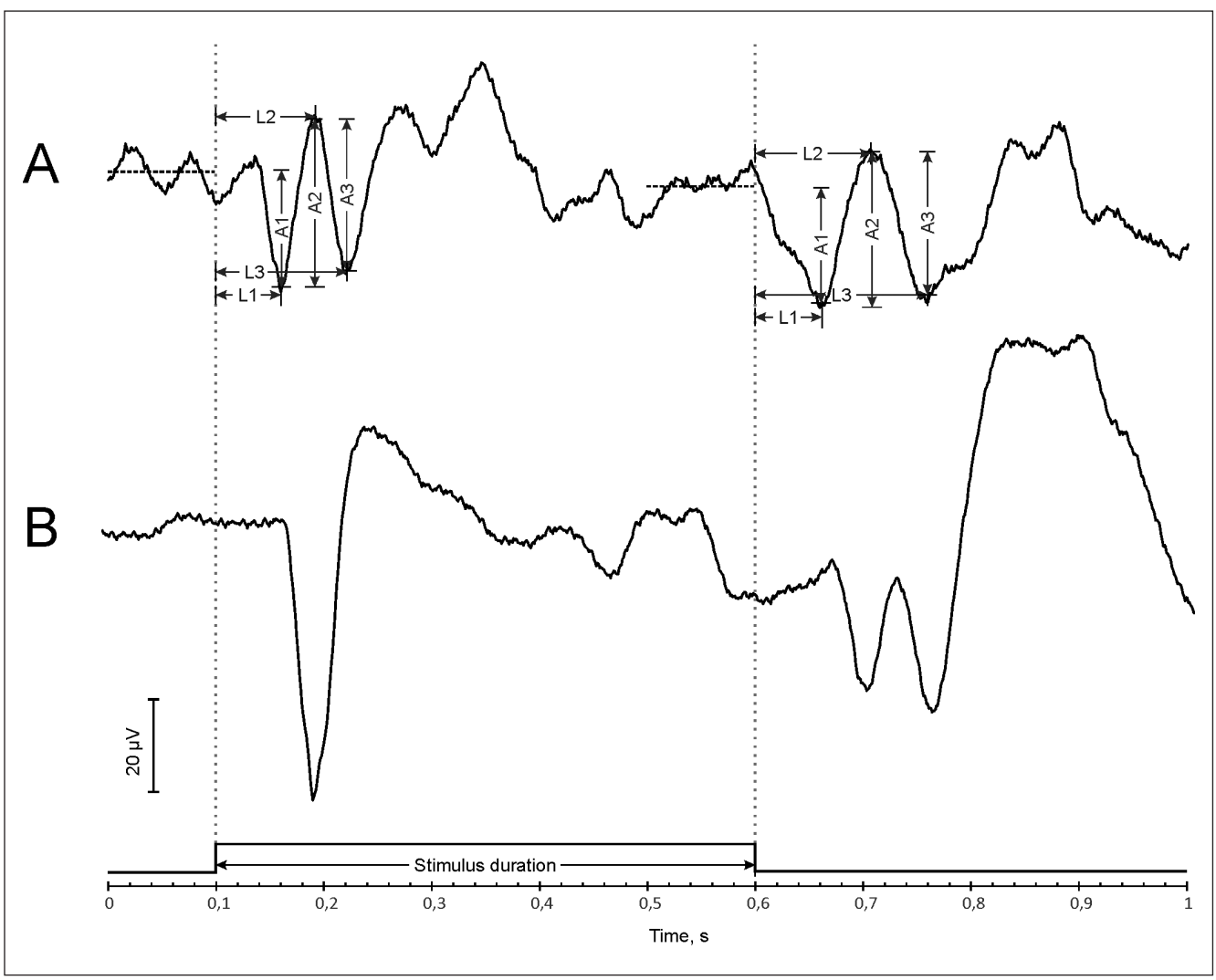

Fig. 1. Example of visually evoked potentials recorded after injection of either (A) saline or (B) 2 g/kg of ethanol during the 4th time bin. Arrows L1, L2 and L3 indicate latency of components N_{63}, P_{89} and N_{143}, respectively. Arrows A1, A2 and A3 indicate amplitude of components N_{63}, P_{89} and N_{143}, respectively. The amplitude of component N_{63} (A1) was measured using baseline-to-peak method, the amplitude of other components (A2, A3) – using peak-to-peak method. The baseline-to-peak amplitude was calculated as the difference between mean voltage of 100 ms before stimulus onset/ offset (horizontal dotted lines) and the peak voltage. The peak-to-peak amplitude was calculated as the difference between two peak voltages. Peak latencies were calculated relative to stimulus onset and offset (vertical dotted lines).

test was performed. The chosen level of significance was $P < 0.05$.

Differences between ON and OFF responses were investigated by analyzing VEPs recorded after application of saline or ethanol (Fig. 1). Our results demonstrated that acute administration of ethanol had a dramatic impact on the latency of the VEP response whereas effect on the VEP amplitude was somewhat weaker (Figs 2, 3).

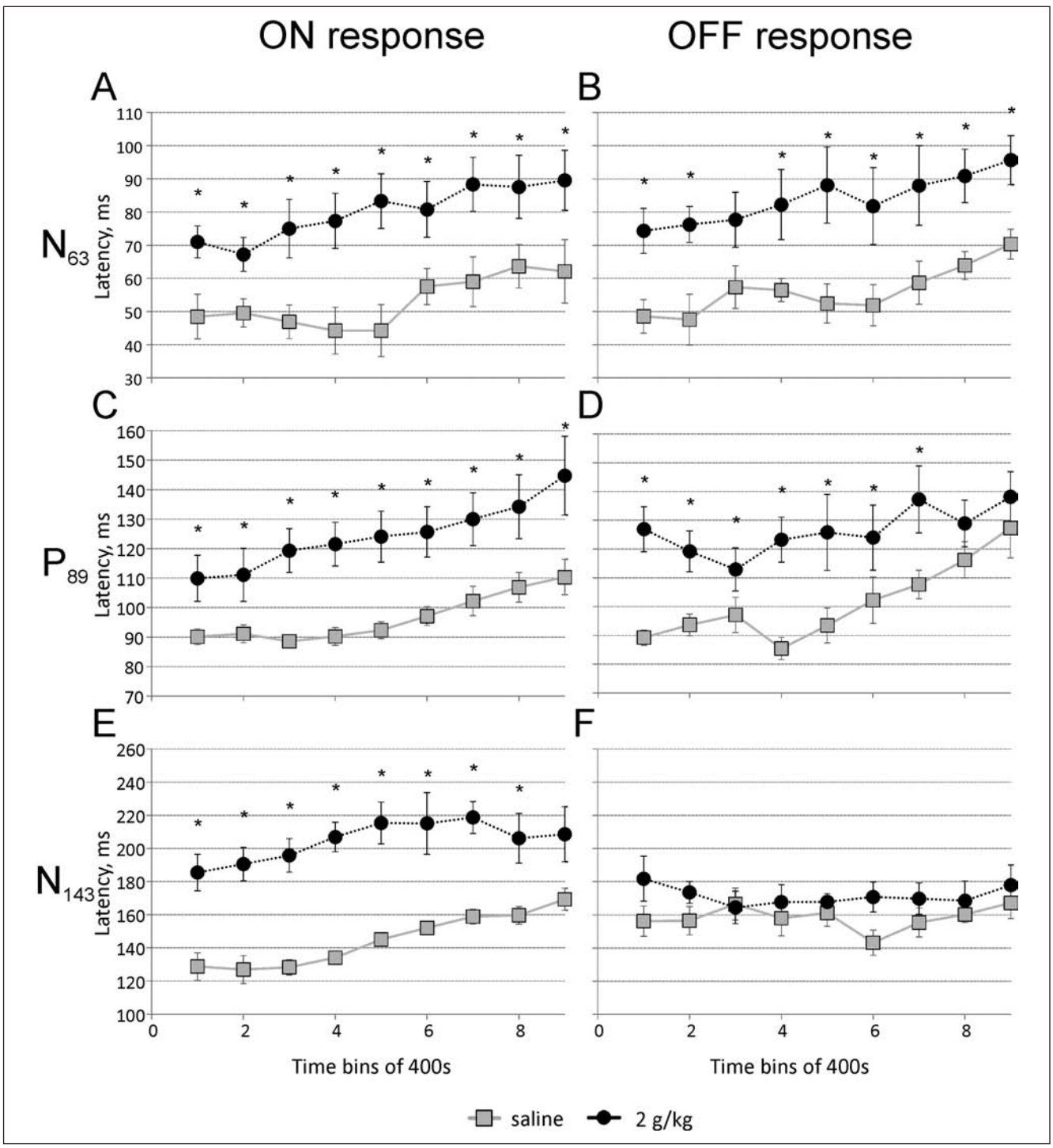

Fig. 2. Latency (ms) of VEP components N_{63} (A, B), P_{89} (C, D), and N_{143} (E, F) following injection of either saline or 2 g/kg of ethanol. One hour recording interval was divided into nine time bins of 400 s. In each time-window, visual stimulus of 500 ms duration was presented 100 times. Peak latencies were calculated relative to stimulus onset (A, C, E) and offset (B, D, F). The data is presented as the average VEPs calculated from 100 responses during each time window. * indicates significant difference between saline and 2 g/kg ethanol, $P<0.05$, error bars indicate S.E.M.

Data analysis revealed that the latency of component N_{63} increased over time during both ON and OFF responses (factor time: $F_{8,242}$=7.6, P<0.001 and $F_{8,242}$=3.6, P<0.01 for ON and OFF responses respectively) (Figs 2A, 2B). Although the pattern of latency dynamics was similar between different treatment conditions, ethanol administration significantly affected the onset response (factor treatment: $F_{2,242}$=31.5, P<0.001). Similarly, the latency of

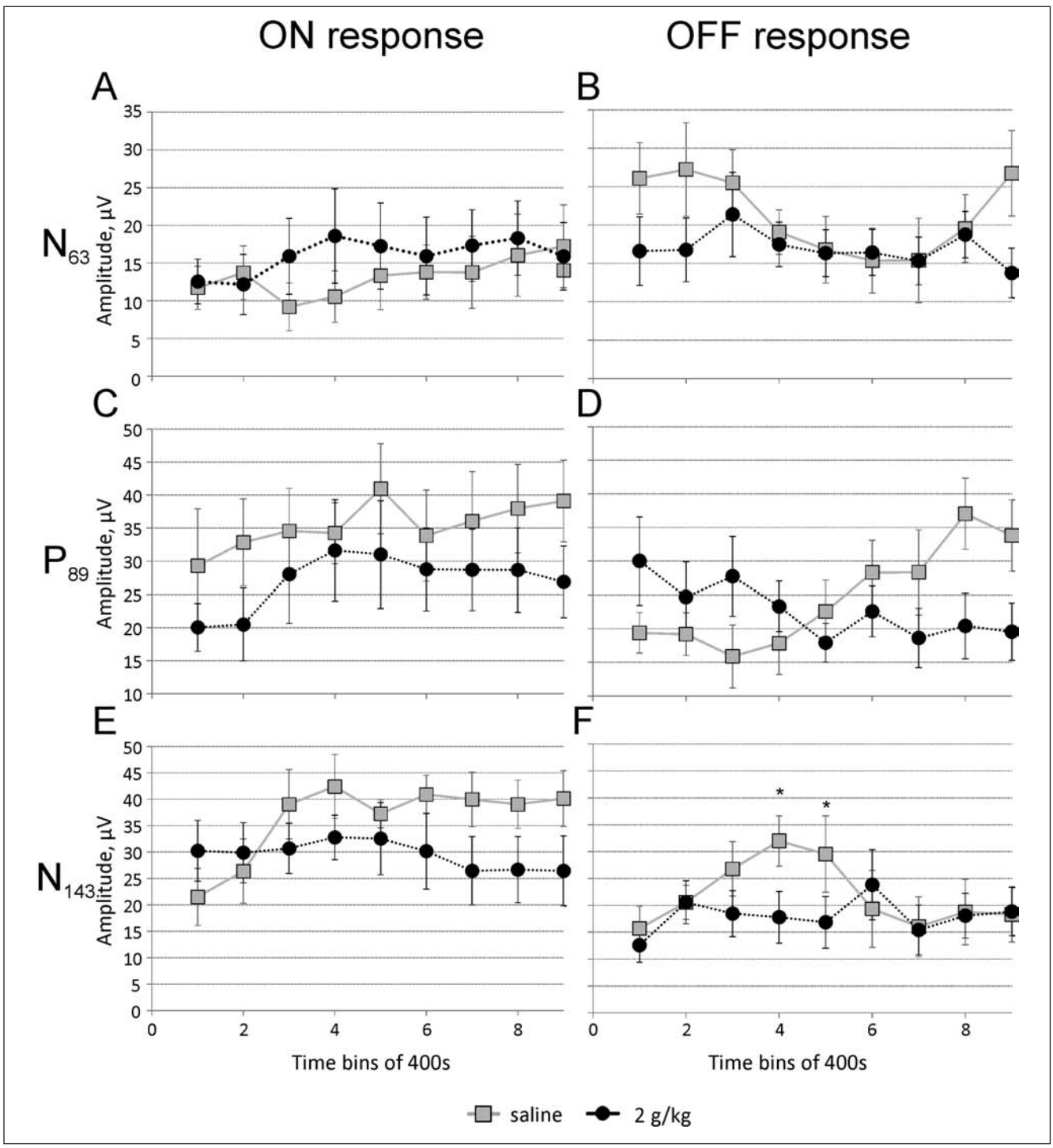

Fig. 3. Amplitude (μV) of VEP components N_{63} (A, B), P_{89} (C, D), and N_{143} (E, F) following injection of either saline or 2 g/kg of ethanol. One hour recording interval was divided into nine time windows of 400 s. In each time-window, visual stimulus of 500 ms duration was presented 100 times. The peak amplitude was calculated relative to stimulus onset (A, C, E) and offset (B, D, F). The data is presented as the average VEPs calculated from 100 responses during each time window. * indicates significant difference between saline and 2 g/kg ethanol, P<0.05, error bars indicate S.E.M.

component N_{63}, elicited by stimulus offset, was longer after alcohol injection than after saline injection (factor treatment: $F_{2,242}$=31.5, P<0.001).

The pattern of latency dynamics of component P_{89} was similar to that of component N_{63} – the latency of P_{89} increased in both treatment groups over the period of one hour (factor time: $F_{8,242}$=15.4, P<0.001 and $F_{8,242}$=3.8, P<0.001 for ON and OFF responses respectively) (Figs 2C, 2D). Administration of ethanol significantly affected the latency during both ON and OFF responses (factor treatment: $F_{2,242}$=14.8, P<0.001 and $F_{2,242}$=15.7, P<0.001 for ON and OFF responses respectively).

The latency of component N_{143} also increased over time in both treatment conditions during ON response (factor time: $F_{8,242}$=9.6, P<0.001) (Fig. 2E), and it was prolonged by ethanol (factor treatment: $F_{2,242}$=11.6, P<0.001). Ethanol administration had no effect on the latency during stimulus offset (Fig. 2F).

Comparison of the latency during ON and OFF responses has shown that the latency of components N_{63} and P_{89} during stimulus onset was not different from stimulus offset following either saline or ethanol injections (P>0.05). The latency of component N_{143} after saline injection changed over time and differed between ON and OFF responses (factor time×stimulus type: $F_{2,162}$=3.7, P<0.001). *Post hoc* analysis showed that, during the first four time bins, the latency during OFF response was longer than during ON response. Administration of 2 g/kg ethanol shortened the latency during the response to stimulus onset compared to the response to stimulus offset (factor time×stimulus type: $F_{1,162}$=6.0, P<0.05).

Analysis of amplitude data has shown that the amplitude of component N_{63}, elicited by stimulus onset, did not change over time and was not affected by ethanol (Fig. 3A). The amplitude during OFF response changed over time (factor time: $F_{8,242}$=2.1, P<0.05), but there were no statistically significant changes induced by ethanol administration (Fig. 3B). The amplitude of component P_{89}, elicited by stimulus onset and offset, did not depend on time or treatment condition (Figs 3C, 3D).

The pattern of amplitude dynamics of component N_{143} is presented in Figs 3E and 3F. A significant effect of ethanol administration was found during ON response (factor time×treatment $F_{16,242}$=2.2, P<0.01), however, *post hoc* analysis revealed that the amplitude increased after saline injection only during the two first time bins. The amplitude decreased after ethanol administration during stimulus OFF response (factor treatment: $F_{2,242}$=5.4, P<0.05 and factor time×treatment interaction: $F_{16,242}$=2.3, P<0.01). *Post hoc* analysis has shown that during the fourth and fifth time bins the amplitude was smaller after ethanol treatment than after saline treatment.

Comparison of ON and OFF responses has shown that the amplitude of component N_{63} during stimulus onset and offset did not differ neither after administration of saline nor after administration of ethanol (P>0.05). Following saline administration the amplitude of the P_{89} component was higher during ON response than during OFF response (factor stimulus type: $F_{1,161}$=6.9, P<0.05). Further analysis has shown that the amplitude was different during the second to fourth time bins. However, administration of ethanol abolished these differences between ON and OFF responses. Finally, different amplitude values of component N_{143} were lower during OFF response than during ON response following administration of saline (the second half of hour) (factor stimulus type: $F_{1,161}$=12.34, P=0.008) and ethanol (the first half of hour) (factor stimulus type $F_{1,161}$=15.6, P<0.01).

The present study demonstrated that acute administration of ethanol caused a considerable increase in latency of nearly all VEP components at the onset and offset of 500 ms visual stimuli in male Wistar rats. We have found that, with the exception of component N_{143}, ethanol affected latency dynamics of both ON and OFF responses in a similar manner. The latency of N_{143} during OFF response was not affected by ethanol. The effect of ethanol on VEP amplitude was not pronounced, significant effect was only found for the amplitude of the N_{143} component.

Our data showed that acute administration of ethanol in anesthetized rats increased the latency of VEP components by more than 30 ms. This increase started 2 min after ethanol administration and remained during the entire one-hour recording time. Previous reports using awake freely moving rats demonstrated that the latency of flash evoked potential components increased 20 min after ethanol administration (Hetzler et al. 1981) and changes of latency components were less than 4 ms (Hetzler and Bednarek 2001, Hetzler and Martin 2006, Hetzler et al. 1981, Hetzler et al. 1988). One factor which could have affected the overall latency of VEP components in our study was anesthesia. It has been demonstrated that the latency of VEP peaks varied depending on the depth of anesthesia with up to 15 ms (Ghita et al. 2013). Both ethanol and sevoflurane acts at the NMDA and GABAa receptors (Nishikawa et al. 2005, Petrenko et al. 2014) and they are also metabolized by the same enzymes (Klotz and Ammon 1998). Interaction of these two compounds could explain such a strong effect of ethanol on the VEP latency in our experiment.

Most of researchers studied the effect of ethanol on visually evoked potentials using short stimulus duration without separating ON and OFF responses. Hetzler and Martin (2006) showed that in freely moving rats ethanol had the strongest effect on FEP components P_{22}, N_{29} and N_{53}, while in the present experiment the strongest effect was recorded on component N_{143}. Based on the assumption that N_{63} and P_{89} results from connections between the superior colliculus, brain stem and diffuse thalamic projections

(Creel et al. 1974), and component N_{143} reflects secondary (or rebound) activation of cortical pyramidal cells (Hetzler and Bauer 2013), our study shows that ethanol produced stronger effect on visual cortex than on subcortical structures. These findings are in accordance with the earlier reports based on FEP recordings (Begleiter and Coltrera 1975, Begleiter et al. 1972).

ON and OFF response latency with and without ethanol did not differ in N_{63} and P_{89} components, which means that at the subcortical level visual processing of stimulus onset is similar to that of stimulus offset. This is in line with studies of other sensory systems – there were no differences found in the latency of auditory N1 component elicited by stimulus onset and offset (Yamashiro et al. 2009). However, analysis of the N_{143} component showed that ethanol affected only the processing of stimulus onset. Following administration of saline, the latency of N_{143} ON response tended to be shorter, compared to the latency of N_{143} OFF response. Ethanol injection increased the latency of ON response, whereas the latency of OFF response was not affected or affected very little. Therefore, it is possible that ethanol interferes with the processing of the stimulus duration at the level of the visual cortex. Single cell recordings showed that the stimulus onset latency varies and depends on the stimulus type which is not the case for the offset latency (Bair et al. 2002, Tadin et al. 2010). Our results extend these findings showing that the stimulus onset is more readily influenced by acute administration of ethanol than the stimulus offset. If ethanol affects perception of stimulus onset without affecting its offset, it is likely that perception of the whole stimulus duration would become shorter. Hence, "drunk" brain will process stimulus onset with longer latency than in normal condition, but if stimulus termination remains unchanged, visual stimulus may be perceived as a shorter one. It was shown that changes in the processing of the stimulus onset and offset interfere with the reaction-time to the sensory input (Hari et al. 1987, Yamashiro et al. 2008, 2009, Serviere et al. 1977). Our data confirm results of previous findings and extends them by suggesting that alcohol has a stronger effect on sensory response to stimulus onset than offset.

Previous research using FEP recordings has shown that the amplitude is sensitive to the effect of ethanol (Begleiter and Coltrera 1975, Begleiter et al. 1972, Hetzler and Bednarek 2001, Hetzler et al. 1981, 1982, 1983, 1988). It is known, that the amplitude of FEP is affected by both small (activating effect) and large (depressant effect) doses of ethanol. However, the results of studies in rats are ambiguous and suggest that the effect of ethanol is different on various FEP components: N_{29}, N_{39}, P_{88}, N_{139}, P_{234} were reduced by ethanol, P_{22}, N_{53}, N_{65} were not affected, and the amplitude of the component P_{46} was increased (Hetzler and Bauer 2013, Hetzler and Bednarek 2001, Hetzler and Martin 2006). In contrast to the effect of ethanol on latency, the amplitude of late components was shown to be more affected by ethanol than the early components (Hetzler et al. 1981). Our findings agree with the results of the earlier research. No effect of ethanol on the amplitude of N_{63} was found in most studies (Hetzler and Bauer 2013, Hetzler and Martin 2006, Hetzler and Ondracek 2007, Hetzler et al. 1981, 2008), whereas the amplitude of the late component was reduced by ethanol, suggesting that the depressant doses of ethanol reduced the response to 500 ms visual stimulus offset in the cortical regions.

In our study, amplitude differences between the ON and OFF responses were seen already following saline application, suggesting that the stimulus onset stimulate the visual system more than the stimulus offset. Indeed, the amplitude of components P_{89} and N_{143} during ON response was higher than that during OFF response, and acute administration of ethanol eliminated (in case of P_{89}) or enhanced (in case of N_{143}) this difference by affecting amplitude of ON response less than OFF response. An increase in the amplitude of the VEP component reflect either stronger sensory information processing or increased arousal in the visual system (Hetzler et al. 2008). Amplitude differences between ON and OFF responses of the P_{89} and N_{143} components show that, contrary to latency, processing of stimulus onset and offset differs at the subcortical and cortical level of the visual system. Ethanol increased responsiveness of the visual system at the subcortical level during OFF response, and eliminated the difference in processing at different stimulus stages. However, at the cortical level ethanol reduced arousal of the visual system during stimulus offset. These changes could be the reason of impaired processing of the visual stimulus, especially during its termination.

In conclusion, application of long-lasting – 500 ms – stimulus enabled us to study the mechanisms of the ON and OFF responses separately. Our study demonstrated that activation of the visual system during ON response to a 500 ms visual stimulus is qualitatively different from that during OFF response. These differences can be measured at both subcortical and cortical levels of the visual system. A depressant dose of ethanol increased the latency of the response to visual stimuli and interfered with the perception of the stimulus duration at the level of visual cortex in a way that perception of the whole stimulus duration became shorter. Analysis of the amplitude of different VEP components showed that ethanol reduced activation of the cortical regions. These changes in the processing of the stimulus onset and offset may interfere with the reaction-time at the behavioral level.

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