Post-withdrawal changes in middle-latency auditory evoked potentials in abstinent human alcoholics

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Received 22 March 1999; received in revised form 9 April 1999; accepted 15 April 1999

Abstract

We investigated the effects of chronic alcoholism on middle-latency auditory evoked potentials (MAEP) in 14 male alcoholics with 1–6 weeks of abstinence (without other severe disorders) and 13 age-matched male social-drinker controls. The peak amplitude of a positive deflection (Pa) of the MAEP, peaking at about 30 ms post-stimulus, was significantly larger in the alcoholics than in the controls (P < 0.01), and notably, a significant negative correlation (r = −0.65) was observed between the Pa amplitude and duration of abstinence in the alcoholics. The present results suggest that the post-withdrawal brain hyperexcitability in the alcoholic brain, gradually recovering with abstinence, could be objectively and non-invasively studied with the MAEP. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Alcoholism; Brain; Electroencephalography; Event-related potentials; Middle-latency auditory evoked potentials; Withdrawal

Alcohol abuse is a major social and health problem with the estimated annual costs in the USA alone exceeding $100 billion [9]. The presence of alcohol-related brain deficits is well-established [4].

Neuropharmacological studies on alcoholism have shown that during a prolonged bout of heavy drinking, neurones gradually adapt to sedative effects of alcohol, and further, that withdrawal leads to brain hyperexcitability caused by reduced inhibition and augmented excitation of synaptic transmission [5,25]. These biphasic effects of alcohol might be detrimental. Previously experienced episodes of ethanol withdrawal have been shown to potentiate the symptoms of subsequent withdrawal [1], further, it has been suggested that the withdrawal related N-methyl-d-aspartate (NMDA) excitotoxicity might contribute to genesis of alcohol-related brain lesions (see Ref. [25]). The relationship between withdrawal hyperexcitability and alcohol dependence has been also extensively studied [10,17]. Further-more, learning theories suggest that subacute alcohol withdrawal syndrome, following acute withdrawal phase, might underlie alcohol craving and thereby precipitate relapse [16].

In the acute withdrawal, many over symptoms of brain hyperexcitability, e.g. psychomotor symptoms or seizures, can be detected in alcoholic patients [8]. Subtle brain hyperexcitability might be, however, detected in alcohols weeks after cessation of the acute withdrawal symptoms [7,15,20,21]. Despite these findings, there is a lack of non-invasive clinical neurophysiological methods for detection and monitoring of the post-withdrawal brain hyperexcitability in vivo in human alcoholics.

The synchronous activity of large neural populations can be studied with auditory evoked potentials (EP), electroencephalogram (EEG) changes time-locked to the presentation of auditory stimuli. Within 10 ms from the stimulus onset, the first ‘far-field’ EP are generated in the brain-stem nuclei. The earliest cortical EP, the middle-latency auditory evoked potentials (MAEP), generated 10–70 ms from stimulus onset, are followed by the late EP components peaking at
100–800 ms. The MAEP is composed of several distinct deflections, the Na peaks at about 25 ms and Pa 30 ms. Intracranial recordings suggest that these deflections are generated in the superior aspects of lateral temporal lobes, in the vicinity of primary auditory cortices [14]. While there is a profusion of research on brainstem and late auditory EP in alcoholism [21], the MAEP have been studied much less extensively.

In keeping with above-mentioned biphasic neuropharmacological effects of ethanol, auditory EP are attenuated and delayed with acute alcohol challenge [11,21], and after withdrawal of chronic drinking, in turn, cortical auditory responses are often enhanced (see Ref. [21]). According to animal [2,3,6] and human [7,20] studies, the withdrawal-related EP enhancement can possibly be detected even weeks after detoxification. The MAEP results in human alcoholics are, however, somewhat discrepant. While post-withdrawal reduction of MAEP peak latencies was found in 1-month abstinent alcoholics by Diaz et al. [7], significant MAEP delaying has also been observed in patients measured ~72 h after detoxification [12]. The patient group of the latter study, however, was unfortunately medicated with central nervous system (CNS) depressants that could have confounded the results, and included also cocaine abusers.

Given the inconsistency of previous MAEP results, we investigated the MAEP changes in alcoholics without CNS depressing medication. Moreover, although the MAEP acceleration, found by Diaz et al. [7], would suggest hyper-excitability-related changes in alcoholics, the possible correlation of this and the duration of their abstinence was not studied. Therefore, to differentiate factors underlying MAEP changes in alcoholics, we studied the correlation between their MAEP, family history of alcoholism, self-reported severity of alcohol abuse, duration of heavy drinking, and duration of abstinence.

Fourteen consecutive male alcoholics meeting DSM-IV criteria for alcohol dependence (29–55 years, mean = 43) that had been abstinent for 7–37 days (mean = 20 days), and 13 age- and education-matched male controls (21–55 years, mean = 37) were studied. An experienced clinician recruited the alcoholics from a routine treatment program. Subjects with hearing loss, neurological, other severe psychiatric, or other severe diseases were excluded. None of the alcoholics had acute withdrawal symptoms (according to Clinical Institute Withdrawal Assessment for Alcohol, CIWA-A [24]).

The alcoholics had been chronically drinking for 1–35 years (mean = 13), and their self-reported weekly ethanol consumption was 336–2520 g (mean = 1232). The control subjects were healthy social drinkers, whose self-reported weekly ethanol consumption was 24–216 g (mean = 106). Alcohol Use Disorders Identification Test, AUDIT [22], was used. The controls abstained from alcohol and other drugs for at least 48 h before the measurement. At the evenings, one alcoholic had mianserin, one had mianserin and promazine, and one had doxepin. The exclusion of these three alcoholics from the analysis had no effect on the results of this study.

The study was approved by the Ethical Committee of the A-Clinic Foundation, Helsinki, Finland. Informed consent was obtained after the procedures had been fully explained to the subjects.

In an acoustically and electrically shielded room, blocks of 4000 click stimuli were binaurally presented 60 dB above the subjective hearing threshold. Offset to onset inter-stimulus interval was 80 ms. Extra-cerebrally referenced EEG (sampling rate 10 000 Hz), measured from bilateral mastoids and electrode sites C5, C6 and Cz (10–20 system), was averaged and digitally filtered (passband 10–250 Hz). Epochs with artefacts exceeding 75 μV at any electrode or at an electro-oculogram were discarded. Group differences

![Fig. 1. (a) Grand-average MAEPs measured from the alcoholics and the controls at electrode site Cz and bilateral mastoids indicating that the Pa deflection was significantly larger in the alcoholics than in the controls. (b) Correlation plot showing a significant negative correlation between abstinence and Pa amplitude in the alcoholics (confidence interval 95%).](image-url)
in the MAEP amplitudes and peak latencies were statistically analyzed with one-way analysis of variance (ANOVA; Statistica 4.1 software, Stat Soft, OK).

Fig. 1 shows that the Pa amplitude measured from the vertex electrode (Cz) was significantly larger \((F(1,25) = 9.07, \ P = 0.006)\) in the alcoholics (mean \(\pm\) SEM = 0.97 \(\pm\) 0.14 \(\mu\)V) than in the controls (0.47 \(\pm\) 0.09 \(\mu\)V). In addition, statistically insignificant augmentation of alcoholic Na amplitude (alcoholics, \(-0.53 \pm 0.15 \mu\)V; controls, \(-0.33 \pm 0.05 \mu\)V), decrease of alcoholic Na peak latency (alcoholics, 18.3 \(\pm\) 0.78 ms; controls, 19.9 \(\pm\) 0.42 ms), and decrease of alcoholic Pa peak latency (alcoholics, 31.2 \(\pm\) 1.36 ms; controls, 34.0 \(\pm\) 1.28 ms) were observed. A significant negative correlation (Fig. 1) was observed between Pa amplitude and logarithm of days of abstinence (Pearson \(r = -0.65, \ P = 0.011\). Pa amplitude did not, however, significantly correlate with self-reported duration or severity of alcohol abuse, or family history for alcoholism.

Previous findings of post-withdrawal acceleration and augmentation of auditory responses were supported by the significant enhancement of the Pa amplitude in the alcoholics \([2,3,6,7,20,21]\). Since the cortical evoked potentials are generally believed to reflect mainly excitatory functions \([18]\), the Pa augmentation could reflect increased neural excitability in the alcoholics, possibly related to post-withdrawal brain hyperexcitability \([5,25]\). Moreover, our novel result demonstrated that the Pa enhancement correlated negatively with duration of abstinence \((r = -0.65)\) in the alcoholics. This suggests that the Pa enhancement reflects at least partially reversible alcohol-related cerebral changes. Recent in vivo benzodiazepine receptor-binding studies suggest that the neuronal changes possibly underlying this residual hyperexcitability could last up to 3 months after detoxification \([15]\), thus constituting a phenomenon of possible clinical relevance.

The present result, however, contradicts the result of Katbamna et al. \([12]\) showing MAEP delaying in recently detoxified alcoholics. Their patients were, however, medicated with NMDA-antagonist amantadine and GABA\(_A\) receptor agonist chlordiazepoxide. This could have confounded their results, since adaptive changes in NMDA and GABA\(_A\) receptor systems is proposed to underlie post-withdrawal CNS hyperexcitability in the alcoholic brain \([5,13,15,25]\).

No significant correlation was observed between MAEP changes and the self-reported duration, or severity of alcohol abuse. Given the inaccuracy of the self-report measures of alcohol drinking, the possible contribution of these variables to the Pa augmentation cannot be excluded. Further, no significant correlation emerged between MAEP abnormalities and family history for alcoholism.

The present results were, of course, obtained with a correlational design, and they should be validated in future studies using a follow-up design where the same patients are repeatedly measured after different lengths of abstinence. Moreover, the MAEP effect could be correlated with post-withdrawal changes in GABA\(_A\)/NMDA receptor densities.

It has been proposed that self-medication of brain hyperexcitability with alcohol might precipitate relapses \([19]\), moreover, benzodiazepines commonly used in withdrawal treatment might increase alcohol craving \([13]\). Therefore, accurate detection of brain hyperexcitability could be beneficial in identification of patients at risk for relapse, and in adjustment of individually appropriate pharmacological interventions. The MAEP are relatively independent of the level of arousal and other endogenous factors such as attention or motivation \([23]\), and could provide an objective marker for detection of post-withdrawal dysfunction in the alcoholic brain.

We thank T. Rinne for technical support. This work was supported by the Finnish Foundation for Alcohol Studies, the Finnish Cultural Foundation and the Academy of Finland.


