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Impaired pre-attentive auditory processing in opioid dependence with and without benzodiazepine co-dependence revealed by combined magnetoencephalography and electroencephalography

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Abstract

Cognitive dysfunctions may be a significant factor in drug-seeking behavior, reducing the efficiency of rehabilitation in opioid dependence. Neurophysiological basis of these dysfunctions is poorly understood. 21 opioid-dependent patients and 15 healthy controls with no experience of illicit drugs were studied with simultaneous electroencephalography (EEG) and magnetoencephalography (MEG). Among opioid dependents 15 were benzodiazepine co-dependent. In a passive oddball paradigm, a train of 700-Hz standard tones (80%), presented to the left ear, was occasionally interrupted by infrequent deviants, which were either 600-Hz or 400-Hz pure tones or complex novel sounds. The auditory evoked potentials (AEP) and fields (AEF) were analyzed. The strength of the N1*m* dipoles was enhanced in patients with benzodiazepine co-dependence, but the latency of the response or the source location was not changed. A delay of mismatch negativity (MMN) response of novel tones in EEG, and delay of P3a*m* response on the contralateral hemisphere to stimulated ear in MEG in opioid-dependent patients were observed. There were no differences in source locations or strengths of the dipoles for P1*m*, MMN*m*, and P3a*m* determined using equivalent current dipoles. There were no group differences in EEG amplitude measures. In conclusion, our results suggest delayed pre-attentive auditory processing of novel information in opioid dependence. Benzodiazepine co-dependence modulated N1*m* response.

Keywords: EEG; MEG; MMN; Opioid dependence

1. Introduction

There is evidence from neuropsychological studies showing that patients with opioid dependence have impairments in attention, working memory, executive functions and concentration (Verdejo-Garcia et al., 2004; Rapeli et al., 2006). The neural basis of perception and cognition can be investigated with AEP and AEF which are time-locked changes to auditory response in EEG and MEG, providing an objective index of auditory processing in the human brain with high temporal resolution.

Only a few EEG studies have investigated the effects of opioid dependence on auditory P3 response, which is reflecting the

Abbreviations: AEP, auditory evoked potentials; AEF, auditory evoked fields; DSM, diagnostic and statistical manual of mental disorders; ECD, equivalent current dipole; EEG, electroencephalography; EOG, electro-oculo gram; MEG, magnetoencephalography; MMN, mismatch negativity; MRI, magnetic resonance imaging; SCID, structured diagnostic interview; HIV, human immunodeficiency virus.

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function of active attentive auditory processing. The studies have shown that patients under the influence of heroin demonstrated normal P3 amplitudes, while during detoxification they showed reduced P3 amplitudes (Kouri et al., 1996). Buprenorphine treatment reversed the P3 amplitudes decrement while no changes were observed in those who received placebo. However, these patients abused also cocaine which could have contaminated the findings. Results of this study were confirmed by Papageorgiou et al. (2004), who found P3 amplitude reduction in heroin addicts. However, motivational factors in these studies cannot be ruled out because P3 is considered as a manifestation of attentional operations and it is elicited during the active task. The response is influenced by subjects attention and arousal (Polich and Kok, 1995).

Neural aspects of pre-attentive auditory processing can be studied by MMN, which is an attention-independent AEP component peaking at about 100–200 ms after stimulus onset (Näätänen, 1992; Kujala et al., 2007). MMN is elicited when a train of frequent standard tones is interrupted by infrequent deviant sounds differing from the standard tone in some respect like frequency, intensity or duration. The auditory system is forming a memory trace of the standard repetitive stimulus in which deviant stimulus is compared. MMN is thought to reflect pre-attentive "automatic" detection of sound change. Further MMN is triggering attention shifting to the stimulus which is in turn thought to be reflected by the subsequent P3a component (Escera et al., 1998).

In a passive odd-ball listening task, MEG selectively measures supratemporal P1*m*, N1*m*, MMN*m* and P3a*m* subcomponents, because they have tangentially located sources in the auditory cortex (Kähkönen et al., 2001). However, P1, N1, MMN and P3a have also radially located sources not visible to MEG, but these can be detected with EEG (Näätänen, 1992). Therefore, combined MEG and EEG technique can provide comprehensive view about drug-induced changes on pre-attentive auditory processing with high temporal accuracy. No studies investigating the effects of opioid dependence on pre-attentive auditory processing have been published yet. Drug challenge studies have shown that monoamine transmitters such as dopamine and serotonin modulate pre-attentive auditory processing studied by combined MEG and EEG (Kähkönen et al., 2002, 2001; Ahveninen et al., 2002; Pekkonen et al., 2002; Kähkönen et al., 2005). These monoamines have a crucial role in cognitive functions (see for reviews, Coull, 1998; Buhot et al., 2000). In turn, functions of the same monoamine systems may be impaired in opioid dependence (Volkow et al., 2002; Gerra et al., 2004, 2003).

In patients with opioid dependence abuse of other illegal substances or prescription medicine, like benzodiazepines is common. For example, in one study 70% of patients with opioid dependence fulfill also criteria of other substance dependence disorder (Ross and Darke, 2000). Benzodiazepines are known to impair active and passive attention studied by MMN and P3 in healthy subjects in single-dose studies (Rockstroh et al., 1991; Javitt et al., 1996; Rosburg et al., 2004; Lucchesi et al., 2005). To our knowledge, no studies exist whether long-term benzodiazepine abuse or dependence affects involuntary attention.

We hypothesized that patients with long-term opioid dependence have impairments of pre-attentive auditory processing as measured with whole-head simultaneous MEG and EEG. Secondly, we expected that opioid dependents with benzodiazepine co-dependence would be more impaired than those without such co-dependence.

2. Methods

2.1. Subjects

Twenty one opioid-dependent patients (8 women, mean age 32.2±6.5 years) participated in this study. Patients had used opioids regularly intravenously from 4 to 26 (mean 10±6) years and from the age of 15 to 31 (mean 18±5) years. During previous years the intravenous self-reported daily doses of street heroin and buprenorphine were 0.05–5 g and 2–32 mg, respectively. 15 patients abused benzodiazepines (approximate equivalent dose to diazepam 38±21 mg (Ashton, 2002)) daily (5 women, mean age 31.5±6.0). Before the study patients gave the urine samples twice a week for minimum of 4 weeks to exclude other illicit substance abuse than opioids or benzodiazepines. They admitted to in-patient drug detoxification unit in Helsinki University Central Hospital for withdrawal and evaluation for methadone maintenance program. The patients were investigated on the day of admission and all had abused opioids during 24 h before the MEG/EEG measurements. All patients met the DSM-IV (Diagnostic and Statistical Manual of mental disorders) criteria for opioid dependence disorder measured with the Structured Diagnostic Interview (SCID) (American Psychiatric Association, 1994; First et al., 1994a,b). In addition to this, 15 patients had the diagnosis of benzodiazepine dependence. Patients were excluded from the study if they had current DSM-IV axis I diagnosis other than opioid and benzodiazepine and/or cannabis dependence disorder. Also 16 patients fulfilled the criteria of DSM-IV for antisocial personality disorder on SCID II and 13 have multiple diagnosis. All patients were in good physical health as determined by a physical examination, laboratory evaluation including a complete blood count, electrolytes, glucose, renal and thyroid analyses. HIV antibody test was negative in all patients tested (one patient refused). All except two of the patients had positive hepatitis C antibody analysis. Hepatic enzymes were mildly elevated in 7 patients and moderately in 1 patient. All patients were tobacco smokers. Brain magnetic resonance imaging (MRI) was obtained from 16 patients and there were no signs of vascular disease (Kivisaari et al., 2004). Fifteen healthy age and sex matched controls (8 women, mean age 31.6±7.4 years) were available in the study. The control subjects had no DSM-IV axis I or II diagnosis in the SCID evaluation. Only one of the controls was smoker. They did not have any experience of illicit drugs including cannabis. Controls used alcohol on social occasions, but they did not meet the criteria of abuse or dependence on alcohol and all were free from psychotropic medication. None had a significant medical illness or a history of central nervous system disease. Brain MRI was normal in all controls.