Alcohol & Alcoholism, Vol. 25, No. 2/3, pp. 251–256, 1990
Printed in Great Britain

0735–0414/90 $3.00 + 0.00
Pergamon Press plc
Medical Council on Alcoholism

NEUROELECTRIC PROCESSES IN INDIVIDUALS AT RISK FOR ALCOHOLISM

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(*Received* 1 *February* 1990)

Abstract — The literature dealing with electrophysiologic research in alcoholics and individuals at risk for alcoholism is reviewed. Event-related potential (ERP) differences between family history positive (FHP) and family history negative (FHN) males have been reported both prior to the ingestion of alcohol and following alcohol challenge doses. At present, the most robust of these electrophysiological findings is the lower P3 amplitude of the ERP, which has now been replicated in several laboratories. This perhaps provides a phenotypic marker, distinguishing those at risk for alcoholism.

For the past two decades our laboratory has been dedicated to the development of event related potential (ERP) methods for the assessment of brain function in abstinent alcoholics. The ERP technique offers a unique approach for assessing multiple levels of brain functioning. Quantitative measurements of salient features extracted from ERP recordings reflect various aspects of brain function related to integrative processes of the brain as well as the functional integrity of different neuroanatomic systems. Indeed, ERP techniques represent an important interface between cellular neurobiology and the behavioral sciences, as well as a unique approach to the study of systems neurophysiology.

Recording neuroelectric activity of the brain has provided a set of techniques quite sensitive to alcohol-related effects such as alcoholization, tolerance, withdrawal, and long-term brain dysfunction (Begleiter and Porjesz, 1979; Zilm *et al.*, 1981). Alcoholization is characterized by significant decreases in the voltages of the ERP (Bierley *et al.*, 1980; Porjesz and Begleiter, 1990*a*) and prolonged P3 latencies (Porjesz and Begleiter, 1990*a*; Schuckit *et al.*, 1988) and conduction velocities of the Brainstem Auditory Evoked Response (BAER) (Squires *et al.*, 1978*a*, *b*; Chu *et al.*, 1978). Chronic alcohol intake is accompanied by ERP voltage reductions and BAER conduction delays which are less pronounced after tolerance has developed (Porjesz *et al.*, 1976; Begleiter and Porjesz, 1977; Chu *et al.*, 1978; Zilm *et al.*, 1981). A number of studies have shown that withdrawal is characterized by increased ERP voltages and decreased BSP latencies indicative of CNS hyperexcitability (Begleiter and Porjesz, 1977, 1979; Begleiter *et al.*, 1980*a*; Chu *et al.*, 1978).

The neuroelectric effects which typically accompany long-term abstinence in chronic alcoholics have been the subject of intensive investigation over the last 15 years. A number of studies have reported prolonged conduction velocities in the BAERs of abstinent alcoholics (Begleiter *et al.*, 1981; Rosenhamer and Silfverskiold, 1980; Chu and Squires, 1980; Chu *et al.*, 1982; Chu and Yang, 1987).

It is important to note that the aforementioned anomalies in conduction velocity were observed in alcoholics abstinent for a relatively short period of time (3–4 weeks). We have conducted longitudinal studies for a limited amount of time (16 weeks post-detoxification) to assess the potential reversibility of those deficits. The alcoholic patients were tested initially 3–4 weeks after admission to the hospital. They remained as inpatients in the hospital for an additional 12 weeks and were retested just before they were discharged from the hospital. The same patients were tested on two separate occasions 3–4 weeks after admission and after 15–16 weeks. All patients were off medication and totally abstinent.

The patients were tested using a variety of ERP techniques including the auditory brainstem potential. We replicated our initial observations (Begleiter *et al.*, 1981) of delayed brainstem transmission time in alcoholics as compared to matched controls. After a total abstinence period of four months we noticed that the BAER anomalies initially observed in these patients were significantly improved (Porjesz and Begleiter, 1985). Indeed we observed improved waveform morphology, significant reduction in peak latencies and improved conduction velocities. The results of our studies suggest that the BAER observations in chronic alcoholics may be the result of alcohol and/or nutritional factors which are in large measure reversible with a sufficiently long period of abstinence and appropriate vitamin supplements.

Evoked potentials have been useful in investigating the function of sensory systems in chronic alcoholics. In addition, a number of investigations have utilized ERPs to assess the functional integrity of higher integrative systems of the brain. Target-selection paradigms have been used for recording ERPs in alcoholics in the auditory (Pfefferbaum *et al.*, 1980; Salamy *et al.*, 1980) and visual (Begleiter *et al.*, 1980*b*; Porjesz *et al.*, 1980, 1987*a*) modalities as well as bimodally (Porjesz and Begleiter, 1979; Patterson *et al.*, 1987). The advantage of using an information-processing ERP design to assess brain functioning is that it provides an opportunity to compare neuroelectric and behavioral responses to identical relevant and irrelevant stimuli that is more revealing about the nature of brain function than the absolute voltage to either stimulus. Control subjects in our study demonstrated an enhanced N1 component to stimuli in the relevant as opposed to irrelevant modality (Porjesz and Begleiter, 1979). In contrast, alcoholics maintained the same low N1 voltage regardless of task relevance.

In other studies we have investigated the late positive component (P3) of the ERP. We examined the ability of abstinent alcoholics to differentiate between relevant and irrelevant events and their ability to probability match stimuli in accordance with their frequency of occurrence. We have repeatedly observed that P3 amplitudes were low or absent in alcoholic patients to rare target stimuli under conditions optimal for eliciting large P3 voltages. This finding was most striking over the parietal area where P3 amplitude is maximal.

The decreased P3 voltages of the ERP observed in our alcoholic patients have been obtained in various studies in our laboratory (Porjesz and Begleiter, 1979, 1982; Porjesz *et al.*, 1980, 1987*a*, 1987*b*; Begleiter *et al.*, 1980*b*) as well as in other laboratories (Pfefferbaum *et al.*, 1987; Patterson *et al.*, 1987; Emmerson *et al.*, 1987). In the past we have assumed that these consistently observed deficits in the P3 voltage of the ERP reflected the consequences of the neurotoxic effects of alcohol on the central nervous system of alcoholic patients.

Recent studies in genetic epidemiology indicate that alcoholism is a highly familial disease. A number of important studies conducted with adoptees (Goodwin *et al.*, 1973; Goodwin and Guze, 1974; Bohman, 1978; Cadoret and Gath, 1978; Cadoret *et al.*, 1980) suggest that for some types of alcoholism it is a heritable disease. Specifically, sons of alcoholic fathers seem to be four times more likely to develop alcoholism than sons of nonalcoholics, even when they are separated from their biological parents soon after birth. As a result of these population genetic findings, we have undertaken a series of investigations for the past several years, to assess the possible presence of neurophysiological anomalies in subjects known to be at high risk for alcoholism.

In our first study, Begleiter *et al.* (1984) hypothesized that deficits in P3 voltage of the ERP may antecede the onset of chronic alcohol abuse and may be present in males at high risk for alcoholism. The investigators decided to test this hypothesis in a select group of individuals who had never had exposure to alcohol and were at high risk for alcoholism according to population genetic studies. ERPs were recorded from twenty-five young sons of alcoholic fathers and twenty-five control boys matched for age, socioeconomic status, school grade, and who had no family history of alcoholism. The experimental paradigm consisted of a complex visual mental rotation task to identify the orientation of a target stimulus. The high risk group showed a significantly reduced amplitude of the late positive component (P3) of the ERP. This pattern of results (low voltage P3 amplitude) is quite similar to results obtained in abstinent alcoholics (Porjesz and Begleiter, 1985), originally presumed to be solely the consequence of alcoholism. These similar findings in ERPs obtained in young, nondrinking sons of alcoholics are particularly interesting because they were obtained without administering alcohol to the subjects.

The reduced P3 voltages of the ERP obtained in young sons of alcoholics have been replicated in an older population. Using the identical experimental paradigm as Begleiter *et al.* (1984), O'Connor *et al.* (1986) recorded ERPs in an older (20–25 years of age) group of sons of alcoholic fathers and matched controls. None of the subjects manifested signs of problem drinking. In agreement with the observations reported by Begleiter *et al.* (1984), these investigators observed a significantly reduced amplitude of the P3 component of the ERP in the high risk males.

Because of the striking similarity in P3 deficits between abstinent alcoholics and males at high risk for alcoholism, Begleiter *et al.* (1987*a*) used the BAER to assess the auditory pathway in young boys at high risk for alcoholism. The investigators examined 23 sons of alcoholics (7–13 years old) and boys matched for age, socioeconomic status and school grade. In contrast to the P3 voltage findings, no significant difference in the BAER was found between high risk and low risk boys. These results suggest that the BAER abnormalities observed in abstinent alcoholics are likely to be the consequence of alcoholism whereas the P3 deficits seen in both abstinent alcoholics and individuals at high risk for alcoholism may be antecedents of alcoholism.

In order to determine if the P3 findings in high risk individuals were modality specific, Begleiter *et al.* (1987*b*) studied auditory evoked potentials in another group of high and low risk boys. An auditory oddball paradigm was developed in which subjects pressed a button to discriminable infrequent stimuli. While the auditory discrimination was a relatively easy sensory discrimination it should be noted that the three interstimulus intervals (0.5, 1.0 and 5.0 seconds) used in the study increased the temporal uncertainty and thus the difficulty of the task. The subjects were 23 young boys (7–16) who were sons of alcoholic fathers and 23 control boys without a family history of alcoholism matched for age, school grade and socioeconomic status. The subjects in this study were carefully interviewed to ascertain that they had no exposure to alcohol or other illicit drugs.

It is important to note that the alcoholic fathers of the young sons tested by Begleiter *et al.* (1987*b*) met the criteria for male-limited (Type 2) alcoholism as proposed by Cloninger (1987). All of the young high risk boys came from families in which familial alcoholism occurred only in males, was highly heritable, gave rise to severe early onset alcoholism with a high rate of recidivism requiring extensive treatment, and was accompanied by the occurrence of petty criminality. These data were obtained by conducting clinical examinations.

The results of this recent study by Begleiter *et al.* (1987*b*) indicate that boys at high risk for alcoholism manifest significantly reduced amplitudes of the P3 component of the ERP. The reduced P3 voltage found in this auditory study indicates that P3 reductions in high risk males does not seem to be modality specific but seems to be present in the visual as well as auditory modality.

These results of reduced P3 voltages in high risk subjects without the administration of alcohol recently have been replicated in three different laboratories: O'Connor *et al.* (1987), by Whipple *et al.* (1988) and by Steinhauer *et al.* (1987) as well as in our own laboratory (Porjesz and Begleiter, 1990*b*). As these findings have now been obtained by various laboratories under different experimental conditions, these results seem to be generalizable. The neurophysiologic deficits observed in young male offspring of male-limited alcoholics are intriguing in light of neurochemical deficits found only in male-limited alcoholics as well as high risk individuals (von Knorring *et al.*, 1985).

Other investigators have reported differences in P3 between high risk and low risk individuals only after the administration of either alcohol or placebo. Elmasian *et al.* (1982) studied the P3 component as well as the slow wave component of the ERP in three separate groups of subjects, each consisting of five matched pairs (five high risk and five low risk); one group served as the placebo group, the second group received a low dose of alcohol and the third group was administered a high dose of alcohol. The subjects were male college students between 20 and 25 years of age who were primarily social drinkers. The investigators observed a significant decrease in the amplitude of the P3 component in the high risk compared to the low risk subjects. However, this finding was only observed after the administration of either alcohol or placebo. The investigators suggest that all subjects expected to receive alcohol; however, only high risk subjects manifested a specific expectancy for alcohol characterized by an unusual brain event. It is also suggested by the investigators that higher than normal alcohol intake in the mothers of high risk individuals might result in altered brain physiology.

Another study conducted in the same laboratory (Neville and Schmidt, 1985) examined the late positive component of the ERP between young adults at risk for alcoholism and low risk individuals. This study did not involve the ingestion of alcohol or placebo, and therefore eliminated expectancy for alcohol as a potential confounding factor. Moreover, the mothers of all subjects were interviewed to determine the use of alcohol and other drugs. Group differences in the late component of the ERP were observed.

In a subsequent study, Schmidt and Neville (1985) recorded ERPs in high and low risk males while they performed a visual language task. All subjects were social drinkers. The investigators found that the amplitude of the N430 component was significantly smaller in men at high risk compared to men at low risk for alcoholism. Moreover, the latency of the N430 was directly related to the amount of alcohol consumed per occasion in the high risk group. These results imply that neuronal function associated with language processes are affected by family history of alcoholism, and the interaction between family history and alcohol consumed per occasion.

More recently we have examined the effects of alcohol in event-related potentials in high and low risk subjects. In order to administer alcohol to male subjects, we selected older (19–25 years of age) individuals than in our past studies. We selected the high risk subjects to include male offsprings (mean age = 22.3) of carefully diagnosed (DSM III-R-RDC) male alcoholics. Moreover, it is important to note that all high risk individuals (N = 25) were selected from alcoholic families with a high density of alcoholic members (mean = 4). This allowed us to exclude sons of alcoholic fathers where the alcoholism might be considered a potentially sporadic case. We excluded individuals with a mother misusing alcohol before, during or after pregnancy. The control subjects were carefully matched to the high risk subjects on the basis of age (mean age = 22.0), height, weight, education and socioeconomic status. The low risk individuals were selected as controls because there was no history of alcohol misuse or alcoholism in any first or second degree relatives. It is important to note that high risk and low risk males were carefully matched on drinking history, which included duration as well as quantity–frequency information.

All individuals were tested one week apart, on three seperate occasions. The order of the conditions (placebo, low dose of ethanol 0.5 ml/kg and high dose 0.8 ml/kg) were randomized across subjects. At this point we have already tested 50 subjects (25 high risk and 25 low risk individuals). Each subject was tested once before the administration of one of three different liquids, and four times subsequent to liquid ingestion: 30, 60, 90 and 120 minutes post-ethanol.

The subjects were engaged in a visual ERP experiment and were asked to identify two targets out of three visual stimuli in a typical P3 paradigm. The frequent non-target stimuli (80%) were vertical lines on a computer display. The two targets were either easy to discriminate (a line deviating from the non-target by 90 degrees) or difficult to discriminate (a line deviating from the non-target by 3 degrees). Each target (easy and difficult) was presented on 10% of the trials. Our results indicate that the ERPs generated by the high risk individuals are significantly different from those obtained by the low risk subjects. Indeed, for both the easy and difficult targets the high risk subjects produced a P3 voltage that was significantly ($P < 0.01$) lower than that produced by the low risk subjects. This result was apparent prior to the administration of alcohol (Porjesz and Begleiter, 1990*b*) as well as post-ethanol ingestion.

These results obtained in young adult males at risk for alcoholism replicate our past findings in young boys at high risk for alcoholism (Begleiter *et al.*, 1984; Begleiter *et al.*, 1987*b*) as well as these findings by O'Connor *et al.* (1986, 1987) and Whipple *et al.* (1988).

It is of interest to note that ERPs appear to be quite heritable (Dustman and Beck, 1965; Polich and Bloom, 1987) and to be rather similar in abstinent alcoholic fathers and their sons (Whipple *et al.*, 1988).

The P3 deficits identified in abstinent alcoholics also discriminate between boys at high and low risk for alcoholism. Therefore as a result of the aforementioned observations we postulate that the ERP deficits we have identified in high risk populations may be quite useful as potential phenotypic markers. The use of reliable and sensitive phenotypic markers may be of great utility in conducting a linkage analysis in large family pedigrees.

Taken together, the neurophysiological studies conducted in populations at high risk for alcoholism indicate rather clear differences between high and low risk individuals. While many questions remain unanswered, these preliminary findings appear quite intriguing and merit further neurophysiological investigations.

In the near future it will become critical to understand the significance of the aforementioned neurophysiological findings in populations at high risk for alcoholism. Indeed we need to assess the potential relationship between neuroelectric deficits in sons of alcoholics and subsequent alcohol misuse and alcoholism. The possible predictive value of electrophysiological deficits in young sons of alcoholics can only be assessed with the use of longitudinal studies in which individuals at high and low risk for alcoholism are tested regularly over several years until they pass through the period of maximum risk for alcoholism.

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