Individuals at Risk for Alcoholism: Neurophysiologic Processes

BERNICE PORJESZ AND HENRI BEGLEITER
Neurodynamics Laboratory
Department of Psychiatry
State University of New York Health Science Center at Brooklyn
Brooklyn, New York 11203

INTRODUCTION AND BACKGROUND

Over the last few decades, electrophysiological aberrations in alcoholics have been extensively investigated with the use of electroencephalograms (EEGs) and event-related-potentials (ERPs) (for reviews, see Begleiter and Platz 1972; Porjesz and Begleiter 1983, 1985). The evoked-potential (EP) or ERP techniques offer a unique approach for assessing level of brain functioning, as electrophysiological activity and cognition can be observed simultaneously. An ERP is obtained by using noninvasive scalp electrodes to record the time-locked electrical brain activity following the delivery of a discrete stimulus to any sensory modality (e.g., auditory, visual). Signal-averaging techniques make it possible both to extract these time-locked neuroelectric signals (ERPs) and to cancel out background random "noise." These time-locked signals represent afferent activity over neural pathways from the generators in the peripheral end organ, to higher integrative centers, to output areas of the brain. The quantification of salient features extracted from ERP recordings provides objective measures of neural processes involved in sensory reception, cognition, and integrative functions, allowing the assessment of the functional integrity of various neuroanatomical systems of the brain.

Recording electrical activity from the brain has proven to be a technique that is differentially sensitive to the various phases of alcohol-related functioning; namely, acute and chronic alcoholization, tolerance, withdrawal, and long-term brain dysfunction characteristic of abstinent alcoholics. Acute alcohol ingestion in humans results in delays in the brain stem auditory evoked response (BAER) (Fukui et al. 1981; Church and Williams 1982), whereas alcohol withdrawal is marked by shortened BAER latencies. In addition, decreases in amplitudes of ERP components (N1–P2) and delays in P3 latencies have been observed following ingestion of alcohol in healthy subjects (for review, see Porjesz and Begleiter 1985). Electrophysiological studies in abstinent alcoholics indicate they have low EEG alpha production and produce an excessive amount of fast frequency activity (Begleiter and Platz 1972; Naitoh 1973; Jones and Holmes 1976). BAER has been found to

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be delayed in alcoholics (Chu and Squires 1980; Rosenhamer and Silfverskiold 1980; Begleiter et al. 1981; Chu et al. 1982; Chu and Yang 1987). Alcoholics manifest low-amplitude P3 components of the ERP to target stimuli (Porjesz et al. 1980, 1987; Patterson et al. 1987; Pfefferbaum et al. 1987). Furthermore, alcoholics manifest delayed N2 components of the ERP. With prolonged abstinence from alcohol, some of these electrophysiological aberrations (e.g., BAER) recover, whereas others (e.g., P3 amplitude) do not (Porjesz and Begleiter 1985).

For many years, these brain aberrations were attributed to the neurotoxic effects of prolonged chronic alcohol exposure, nutritional deficits, or an interaction of alcohol and nutrition-related factors. More recently, the evidence is amassing that some of these electrophysiological aberrations may antecede the development of alcoholism and may be related to a genetic predisposition to alcoholism.

There is increasing evidence from population genetic studies that certain individuals are at risk for developing alcoholism. Specifically at higher risk seem to be sons of alcoholic fathers, who are four times more likely to develop alcoholism than sons of nonalcoholic fathers (Goodwin and Guze 1974; Goodwin 1979), even when they are separated from their biological parents soon after birth (Cloninger et al. 1981). Studies of male adoptees in Scandinavia indicate that the biological rather than the adoptive parent is predictive of later drinking problems (Goodwin et al. 1973; Goodwin and Guze 1974; Bohman 1978; Cadoret and Gath 1978; Cadoret et al. 1980). Furthermore, the concordance rate for alcohol abuse between identical twins is almost double the rate for fraternal twins (Kaij 1960), and patterns of alcohol consumption have been reported to be highly concordant among identical twins (Partanen et al. 1966; Jonsson and Nilsson 1968; Loehlin 1972). Taken together, these population genetic studies suggest that genetic factors predispose sons of alcoholic fathers to alcoholism.

The identification of genetically transmitted biological marker(s) would provide more definitive evidence that the etiology of alcoholism involves genetic factors. In addition, it could perhaps elucidate the potential nature of these genetic factors. There is a good deal of evidence that characteristics of both the EEG and ERP are genetically determined; e.g., the production of fast EEG activity has been demonstrated to be genetically transmitted (Vogel 1970; Young et al. 1972; Propping 1977). In various studies, Vogel has reported on the hereditary nature of several EEG variants (monomorphic alpha, low-voltage EEG, EEG with alpha and beta diffusely mixed, EEG with fronto-precentral beta) (Vogel 1970; Vogel et al. 1986). He maintains that the low-voltage and regular alpha EEG are inherited via an autosomal dominant mode, whereas the poor alpha or diffuse beta variants are under polygenic control (Vogel 1970). EPs recorded to flashes of different inten-

sities have been reported to be under genetic control (Buchsbaum and Pfefferbaum 1971). Monozygotic twins manifest EP waveforms that are as concordant with each other as EPs obtained from the same individual tested twice (Dustman and Beck 1965; Surwillo 1980). The P3 component of the ERP is more similar in identical twins than in controls (Polich and Burns 1987).

It is quite likely that a genetic predisposition to alcoholism is manifested in brain function, and it is possible that electrophysiological events may serve as biological markers. Therefore, investigating these genetically determined electrophysiological measures of brain function provides an important approach to the study of possible genetic factors in alcoholism.

EEG

For the last several decades a number of investigators have observed that resting-state EEG activity recorded from awake abstinent male alcoholics manifests an overabundance of high-frequency activity (beta, fast EEG) and a deficiency in lower frequency EEG activity (e.g., alpha) (for review, see Begleiter and Platz 1972). The production of fast EEG activity has been demonstrated to be genetically transmitted (Vogel 1970; Young et al. 1972; Propping 1977).

These EEG findings in alcoholics, coupled with the population genetic studies of alcoholism, suggest that subjects at risk for alcoholism (male offspring of male alcoholics) would be more likely to manifest an excess of fast EEG activity. Gabrielli et al. (1982) tested this hypothesis in a sample of 27 Danish children of alcoholics compared with children of nonalcoholics. As hypothesized, they observed that male (but not female) offspring of alcoholics manifested fast EEG activity compared to controls.

A number of studies in subjects at risk for alcoholism have investigated EEG responses to alcohol. In one study, Pollock et al. (1983) report that high risk (HR) sons of alcoholics (19–21 years old) exhibit more changes in alpha activity after ingesting 0.5 g/kg of alcohol compared to low risk (LR) subjects. After alcohol ingestion, HR subjects manifested greater decreases in fast alpha activity (9.75–12.10 Hz) and greater increases in slow alpha activity (7.42–9.46 Hz). The decreases in fast alpha activity were observed at 120 minutes post-ethanol, and the increases in slow alpha were observed at both 90 and 120 minutes. In addition, HR subjects manifested greater decreases in alpha frequency than did LR subjects at 30, 60, and 120 minutes after alcohol administration.

Despite the earlier findings from their group (Gabrielli et al. 1982) that sons of alcoholic fathers produce excessive beta activity without ingesting alcohol, Pollock et al. (1983) did not report any EEG differences between

HR and LR groups prior to ethanol ingestion; furthermore, their analyses were limited to theta and fast and slow alpha activity, and beta activity was not discussed. In a subsequent paper, Pollock et al. (1984) did not replicate Gabrielli's findings. Although the HR subjects did not report a higher amount of alcohol consumption than LR subjects, they reported needing significantly more drinks to "feel tipsy." These results suggest that HR subjects are more sensitive to the physiological effects of alcohol and less sensitive to its subjective effects.

Another group of investigators has reported that males with family histories of alcoholism have more power in the fast frequency alpha range (9–12 Hz) than males without family histories of alcoholism, prior to alcohol ingestion (Ehlers and Schuckit 1990b). Family history positive (FHP) males responded less intensely to an ethanol challenge than family history negative (FHN) males in terms of the stability of their fast frequency of alpha. Furthermore, Ehlers and Schuckit (1990a) report that FHP men manifested more beta (12–20 Hz) activity than did FHN men, 90 minutes post-ethanol. In the FHN group,"moderate" drinkers were found to have more energy in the beta frequency range than the "low" drinkers, both at baseline and at 90 minutes post-ethanol. In contrast, no differences in beta activity between "low" and "moderate" drinkers were found in the FHP group.

Both laboratories have investigated fast frequency alpha activity in subjects at risk for alcoholism, but their EEG findings are different. Ehlers and Schuckit (1990b) report less physiological responsiveness and "sensitivity" to ethanol in the FHP compared to the FHN group, whereas Pollock et al. (1983) report more responsiveness and more sensitivity. Yet both groups agree that HR males report feeling less intoxicated after a single dose of alcohol (Schuckit 1980, 1984; Pollock et al. 1983).

In another interesting study, Pollock et al. (1988) attempt to resolve the issue of physiological and subjective sensitivity by testing two hypotheses, namely:

1. HR subjects will manifest greater physiological change and less subjective sensitivity to alcohol compared to controls (Tarter et al. 1984). Tarter et al. (1984) speculate that pre-alcoholics are particularly vulnerable to the effects of alcohol; they exhibit a great deal of physiological lability, and alcohol may regulate their physiological functioning. They have difficulty identifying their subjective states because of this physiological lability.
2. HR subjects will manifest less physiological and subjective sensitivity to alcohol (Goodwin 1981). Goodwin (1981) speculates that in order to develop alcoholism, individuals possess high initial tolerance for alcohol effects (defined as individual variation in sensitivity to alcohol, not acquired tolerance associated with development of dependence).

To test these hypotheses, Pollock et al. (1988) divided a sample of FHP males into those exhibiting the most EEG change (in terms of mean alpha frequency) following ethanol administration, and those exhibiting the least EEG change (similar to controls). They found that the two groups differed in terms of the time course of their subjective ratings. The group manifesting the most EEG change differed from controls at 55 but not 25 minutes post-ethanol, whereas the group manifesting the least EEG change differed from controls at 25 but not 55 minutes post-ethanol. The group with the least EEG change did not report higher levels of intoxication at 25 than at 55 minutes post-ethanol, whereas both the controls and subjects with the greatest EEG changes did.

The characteristics of the groups manifesting the greatest EEG change can be related to Tarter's hypothesis, and those manifesting the least change can be related to Goodwin's hypothesis. However, Tarter's hypothesis about physiological lability was not adequately addressed in this study, as neither placebo data nor measures of within-subject variability of mean alpha frequency were obtained.

Since differential responses to ethanol challenge have been reported depending on an individual's pre-ethanol resting EEG signature (Propping 1983), it is important to ascertain whether there are EEG differences between HR and LR groups prior to alcohol ingestion. Propping (1983) found that subjects manifesting poor alpha activity prior to ethanol manifested the most synchronization following alcohol, whereas those with regular pre-ethanol alpha exhibited slight change. Thus the effect of alcohol on EEG depends on pre-alcohol EEG pattern, which is under genetic control. Propping (1983) maintains that EEG with poor alpha or beta reflects a stronger ascending reticular activating system. As mentioned previously, Vogel (1970) has identified different genetic EEG patterns. He postulates that low-voltage and regular alpha are autosomal dominant, whereas poor alpha and diffuse beta are under polygenetic control. On the basis of the work of Propping (1983), it would seem that subjects with poor alpha or beta in their pre-alcohol EEG are more susceptible to ethanol effects. Therefore, it is important to know if Pollock's HR sample consisted of more subjects manifesting more beta activity and poor alpha than the LR group—perhaps explaining their greater response to alcohol.

In addition, it is important to characterize the EEG in the control groups before alcohol, since they may consist of individuals with different EEG variants as well. Possibly the lack of agreement between EEG laboratories is a function of differences in the EEG patterns in the subjects forming both their control and HR groups.

Because alcoholics have been reported to have poorly synchronized EEG, it can be postulated that their offspring would be more likely to inherit this

pattern. However, Propping et al. (1981) found that female and not male alcoholics manifested this poorly synchronized EEG pattern, as did their relatives.

Taken together, the aforementioned findings indicate that alcoholism is not a homogeneous disease and suggest that subjects at risk may be characterized by different EEG patterns. Perhaps the alcoholics with desynchronous resting EEG (predominantly females) represent a group that uses alcohol to relax and synchronize their alpha activity (Cloninger's type 1) (Cloninger 1987), thus normalizing their physiological functions. These alcoholics probably correspond to Pollock's HR group that are more responsive to alcohol, and are most likely more labile, supporting Tarter's hypothesis. Alcoholics with stable synchronous EEG are probably those who are not as responsive to alcohol; this corresponds to Ehlers's FHP group as a whole, and to Pollock's HR subgroup that show less responsiveness. However, until studies are performed in which EEG patterns are characterized before and after ethanol and placebo challenges, these conclusions remain speculative.

ERP

The ERP is a very sensitive index of the functional integrity of the brain. In addition to being sensitive to sensory aspects of information processing, ERP techniques have proven to be very useful in indexing electrophysiological concomitants of complex cognitive tasks (Donchin et al. 1978; Hillyard et al. 1978; Donchin 1979). ERPs consist of characteristic, highly reproducible waveforms lasting between 250 and 500 milliseconds. The early components (less than 100 msec) of the EP reflect stimulus characteristics (e.g., intensity), whereas the later components are more influenced by psychological factors. ERPs can be recorded in conjunction with behavior, or even when no behavioral response is required; they can be recorded to attended and unattended stimuli. Because the ERP is sensitive to genetic (Polich and Burns 1987), sensory, cognitive, and motor aspects of information processing, it can be a valuable tool in studying the genetics of alcoholism.

A great deal of attention has focused on the P3 component of the ERP, a prominent positive component occurring between 300 and 500 milliseconds after the stimulus, related to stimulus significance. We have investigated P3 with numerous paradigms and have reported that it is markedly reduced or absent in abstinent alcoholics. Although other ERP component differences in alcoholics (e.g., BAER) reverse with prolonged abstinence, reduced P3 amplitudes do not (Porjesz and Begleiter 1985).

For the last decade, our laboratory has studied ERPs in subjects at risk for alcoholism. In our first study, the HR group consisted of boys between the ages of 7 and 13 who had no prior exposure to alcohol (Begleiter et al. 1984).

In each case, the father had received a diagnosis of alcoholism (DSM-III) and had been in treatment for alcoholism at some time. We excluded boys whose mothers had either ingested alcohol during pregnancy or who drank excessively after birth. Only boys with neither medical problems nor exposure to alcohol or other substances of abuse were included in this study. The LR group consisted of healthy normal boys matched for age and socioeconomic status to the HR subjects. They were included only if they had no prior exposure to alcohol or other substances of abuse, and if they had no first- or second-degree relatives with a history of alcoholism or other psychiatric disorder. With the exception of family history of alcoholism, the same exclusion criteria were used in both the LR and HR groups.

A complex visual P3 head-orientation paradigm was used. The target stimulus was a rarely occurring aerial view of the head with the nose and either the right or left ear drawn in, rotated in one of two possible positions. This yielded four possible targets, namely: nose up and right ear, nose up and left ear, nose down and right ear, nose down and left ear. These targets were interspersed randomly among non-targets (ovals). Subjects were required to press one of two microswitches to the targets, as quickly and accurately as possible, indicating whether the right or left ear was presented. In the "easy condition," the head was facing forward (nose up on screen) and the left or right ear appeared on the same side as the appropriate button; in the "difficult" condition, the head was facing back (nose down on screen) and the left or right ear appeared on the side opposite the corresponding button.

P3 amplitudes were significantly smaller in the HR compared to the LR groups to all target stimuli. This group difference was most significant at the parietal electrode (where P3 is maximum) for the difficult condition. Principal component analyses with Varimax rotation (PCAV) performed on the data indicated that only the factor representing the P3 component was significantly different between the HR and LR groups.

This study was the first in the field to indicate that P3 amplitude is significantly reduced in boys at risk for alcoholism, without exposure to alcohol. Since this original study, several laboratories, including our own, have replicated these findings; namely, O'Connor at the University of Connecticut, Whipple at UCLA, and Steinhauer at the University of Pittsburgh. O'Connor et al. (1986) replicated the findings of Begleiter et al. (1984) using the identical head-orientation paradigm; specifically, they reported reduced P3 amplitudes without the administration of alcohol in an older group of HR males.

Begleiter et al. (1987b) studied another group of sons of alcoholics to determine whether the reduced P3 amplitudes observed in HR subjects was task- or modality-specific. A modified auditory oddball task was used, in which subjects pressed a button in response to rarely occurring tones pre-

sented at a random rate; accuracy was stressed over speed. Twenty-three matched pairs of FHP and FHN males between the ages of 7 and 16 were studied; they were carefully interviewed to ascertain that they had no exposure to alcohol or illicit drugs.

The fathers of HR boys in this sample met the criteria for male-limited (type 2) alcoholism (Cloninger 1987). They manifested early-onset alcoholism and a high rate of recidivism, often accompanied by petty criminality, and they required extensive treatment. Additionally, the HR boys came from families in which alcoholism was highly heritable and was limited to males.

As in the previous visual study, the FHP boys manifested reduced P3 amplitudes. The reduced P3 voltages in HR males in this auditory paradigm suggest that these reduced P3 voltages are not task- or modality-specific; they seem to be present in auditory and visual paradigms under conditions of speed and accuracy.

Another laboratory (Whipple et al. 1988) used a continuous performance test (CPT) to examine ERPs in prepubescent boys at high risk for alcoholism. This visual paradigm consisted of a complex series of visual stimuli that changed along three dimensions: shape, color, and identity of a number. The subject silently counted each time a stimulus identically matched the one preceding it on all three dimensions. In agreement with both Begleiter et al. (1984, 1987b) and O'Connor et al. (1986, 1987), Whipple et al. (1988) report a reduction in the amplitude of the late positive complex (LPC), including a P3 component.

In our own laboratory, we have recently replicated our original findings of reduced P3 voltages without the administration of alcohol in an older sample (18–23) of sons of male alcoholics (Porjesz and Begleiter 1990). The sample consisted of 25 male offspring of carefully diagnosed (DSM-IIIR/RDC) male alcoholics and was selected from high-density alcoholic families (mean number of alcoholic family members = 4). Thus, sons of alcoholic fathers were excluded in cases where alcoholism may have been sporadic. Furthermore, individuals with mothers who abused alcohol before, during, or after pregnancy were excluded. Controls were matched to the sons of male alcoholics on the basis of age, education, and socioeconomic status. They were selected from families in which there was no history of alcohol abuse or alcoholism in any first- or second-degree relatives. FHP and FHN subjects were carefully matched on drinking history, including duration and quantity-frequency information.

We used a different visual-spatial paradigm involving easy and difficult line discriminations. Previously we had demonstrated that abstinent alcoholics manifested reduced P3 amplitudes with this design. The stimuli consisted of a non-target (vertical line) and two targets: an easy target that deviated from vertical by 90 degrees (horizontal line) and a difficult target that deviated

from vertical by only 3 degrees. The subject pressed a button as quickly as possible (reaction time [RT]) to all non-vertical stimuli.

The results indicated that prior to alcohol ingestion, P3 amplitude is significantly lower in HR subjects compared to controls. This replicates our previous findings (Begleiter et al. 1984, 1987b) of lower voltage P3s in an older sample of HR males as well as the findings of O'Connor et al. (1986, 1987) and Whipple et al. (1988). The largest differences in P3 amplitude between groups occurred to the easy target, to which LR subjects manifested extremely high voltages. These results are the same as those we obtained in alcoholics with the same paradigm where the easy target elicited the greatest significant difference in P3 amplitude between groups (Porjesz et al. 1987). This P3 amplitude difference between groups was most apparent at Pz and Cz electrodes.

Most recently, in another auditory target selection task, we have observed that adolescent HR males manifest lower amplitude P3s than LR males (B. Porjesz and H. Begleiter, in prep.). In this paradigm (modified after Hillyard et al. 1978), rare or frequent tones were randomly presented rather quickly (600–800 msec) to either the right or left ear. The rare tones to a specific ear were designated as targets, and the subject pressed a button to these as quickly as possible. The same rare tones to the other ear were ignored. In the absence of other differences between groups (N1 amplitude), HR males manifested lower amplitude P3 components to targets.

The amplitude of P3 to both the rare attended (P3b) and unattended (P3a) tones were of lower voltage in HR subjects, indicating that HR subjects do not make probability matches as well as controls. In an inattention auditory oddball paradigm, we have also found that P3a is of lower amplitude in HR adolescent males. In this experimental design, subjects read a book while rare and frequent tones were randomly presented binaurally via headphones.

Taken together, the foregoing results examining P3 amplitudes indicate they are reduced in voltage in HR males both to attended and unattended stimuli, and to easy and difficult discriminations in visual and auditory modalities. Despite the general consensus that P3 amplitudes are of lower voltage in HR males, some studies have failed to replicate these findings. Polich and Bloom (1987, 1988) and Baribeau et al. (1987) have not observed significantly reduced P3 amplitudes in sons of alcoholics.

Baribeau et al. (1987) examined HR and LR subjects who were further subdivided according to the amount of alcohol they consumed (heavy vs. light drinkers). They used an auditory selective attention paradigm in which rare (500 Hz) and frequent (600 Hz) tones were randomly presented to either the right or left ear at a random rate (630–880 msec). Subjects were instructed to count the signals in one ear and ignore those in the other ear.

Although HR subjects did not exhibit reduced P3 amplitudes, the light

drinkers manifested insignificantly smaller P3s in the *inattention* condition. These results suggest that when attention is mobilized, P3 deficits are not apparent in the attended channel. Perhaps the lower P3 amplitude in the unattended channel would reach significance with a larger number of subjects. As mentioned previously, we have found reduced P3 amplitudes to rare tones in the unattended channel in HR subjects with a Hillyard paradigm similar to the one described by Baribeau et al. (1987).

HR subjects manifested significantly larger N100 components than did LR subjects in the attention condition; this perhaps indicates that the HR subjects paid more attention than the LR subjects to the stimuli. Furthermore, it is possible that the HR subjects find the tone discrimination task more difficult than the LR group (500 Hz vs. 600 Hz) and hence need to pay more attention.

Finally, it seems that the subject sample represents an older group of HR individuals. There is a rather large age range (19–35) with mean ages of 27 (HR, heavy drinking), 22 (HR, light drinking), 24 (LR, heavy drinking), and 25 (LR, light drinking). It seems that these HR subjects may have passed the age of risk, and perhaps the sample is not representative of a group at high risk for alcoholism, considering that those who already manifested alcoholic problems were excluded. If by this age they have not developed alcohol-related problems or become alcoholic, the likelihood is that they will not, and this represents a skewed sample of HR subjects, perhaps endowed with protective mechanisms. Certainly, their larger N100 component suggests they are atypical. In a P3 study by Hill et al. (1988), increased cognitive efficiency in nonaffected siblings of alcoholics was reported. They observed shorter P3 latencies in these nonaffected siblings, and they suggest that this offers protection against the development of alcoholism.

In various studies at the University of California at San Diego examining ERPs in college students with positive family histories of alcoholism, conflicting ERP results have been reported. This is mostly the work of Neville (Elmasian et al. 1982; Neville and Schmidt 1985; Schmidt and Neville 1985) and Polich (Polich and Bloom 1986, 1987, 1988; Polich et al. 1988; Schuckit et al. 1988).

Following the administration of either alcohol or a placebo, differences in P3 characteristics have been found between subjects at high risk and at low risk for alcoholism. Elmasian et al. (1982) studied the P3 and slow-wave components of the ERP in HR and LR male college students (ages 20–25) under placebo, low doses, and high doses of alcohol. Unfortunately, different sets of subjects were used for each dose, and there were only five pairs of subjects per group.

After alcohol or placebo administration, Elmasian et al. (1982) reported significant P3 amplitude decreases in the HR compared to the LR subjects.

They explained their results in terms of differential expectancies for alcohol characterized by different brain events and also suggested that the results may be due to higher than normal alcohol intake in the mothers of the HR subjects.

In a subsequent study in the same laboratory (Neville and Schmidt 1985), the LPC of the ERP in HR individuals was investigated without the ingestion of any liquid. In this study, mothers of all subjects were interviewed with respect to their alcohol and drug use, and the experimental design eliminated expectancy effects. Group differences in the LPC were still observed between groups.

In another study, Schmidt and Neville (1985) investigated ERPs in HR males while they were engaged in a visual language task. They found that the N430 component (a component related to semantic processing) was significantly smaller in men at high risk for alcoholism than in men at low risk. Moreover, in the HR group, the latency of N430 was directly related to the amount of alcohol consumed per occasion. These fascinating results imply that neuronal function associated with language processes is affected by family history of alcoholism and that there is an interaction between family history and alcohol consumed per occasion and N430.

Investigating ERPs in male college students with and without family histories of alcoholism, Polich and Bloom (1987, 1988) and Schuckit et al. (1988) did not find P3 amplitude differences between groups. Schuckit et al. (1988) did not find any ERP differences between FHP and FHN subjects prior to ethanol ingestion or following a placebo dose, using an auditory oddball paradigm. Following a high dose of ethanol (1.1 ml/kg), P3 latency delays returned to baseline measures more rapidly in FHP men. This suggests that some electrophysiological differences between FHP and FHN individuals are apparent only in response to ethanol challenges, perhaps representing innate tolerance in the FHP subjects.

The initial placebo effect in FHP subjects (Elmasian et al. 1982) was not replicated in the same laboratory (Polich and Bloom 1988). These ERP results may be spurious, since they involve very small sample sizes. Elmasian et al. (1982) tested only five subjects per group, and Polich and Bloom (1988) tested only ten subjects per group.

An inverse correlation between the amount of alcohol consumption (drinks per sitting) and the amplitude of P3 was found by Polich and Bloom (1987) without the administration of alcohol. However, this relationship was only apparent for a difficult intensity discrimination task in FHP subjects. Although there was a trend in this direction in FHN subjects, it was not significant. The authors concluded that FHP subjects are more sensitive to the effects of alcohol than are FHN subjects. When a similar intensity discrimination study was performed in the visual modality, no correlation between P3

characteristics and amount of alcohol typically consumed was found (Polich et al. 1988). Furthermore, in yet another study designed to replicate Elmasian et al. (1982), Polich and Bloom (1988) not only did not replicate their previous findings of a placebo effect in the FHP group, but also now reported that in both FHP and FHN subjects there was a correlation between P3 *latency* and amount of alcohol consumption.

These findings relating alcohol consumption to P3 characteristics therefore do not appear to be robust. In the same laboratory, using samples drawn from the same basic population of students, their findings are not readily replicable. Previous alcohol consumption has been found to correlate with P3 amplitude only, particularly in FHP subjects (Polich and Bloom 1987), to correlate with P3 latency only (Polich and Bloom 1988), and to be uncorrelated with any previous drinking variables (Polich et al. 1988). The relationship between P3 characteristics and drinking history is as yet an unresolved issue in other laboratories as well. O'Connor et al. (1986) report no relationship between any P3 characteristic and drinking history, whereas Steinhauer et al. (1987) report a correlation between drinking history and P3 latency. In addition to correlations between P3 characteristics and drinking history, N430 latency has been reported to correlate with number of drinks per occasion in HR subjects (Schmidt and Neville 1985).

One possible explanation for the lack of results in the San Diego group is the mode of assessment of alcoholism in the fathers, and the clinical assessment of their families in general. A questionnaire is filled out by the son about his father's alcohol and psychiatric history and that of his first- and second-degree relatives. Unconventional criteria regarding the father's alcoholism are employed (a single positive symptom), and no verification of family history by other family members is used. Thus, it is possible that in a large percentage of subjects, the offspring are not offspring of alcoholics but of heavy or moderate drinkers. This weakens the possibility of obtaining ERP differences between FHP and FHN groups. Therefore, it is conceivable that there is more agreement in the literature dealing with subjects at risk for alcoholism than had been heretofore suspected.

Although it has been hypothesized that discrepancies in results between laboratories may be due to task difficulty, recent evidence fails to support this contention. O'Connor et al. (1987), using two tasks at different levels of task difficulty, obtained identical results with both paradigms. Begleiter et al. replicated their finding of a lower P3 amplitude in HR subjects without the ingestion of alcohol in four different paradigms thus far; namely: a complex visual response-compatibility/incompatibility design (Begleiter et al. 1984), an auditory modified oddball paradigm (Begleiter et al. 1987b), a visual discrimination paradigm (Porjesz and Begleiter 1990), and an auditory Hillyard paradigm (B. Porjesz and H. Begleiter, in prep.).

More recently, we investigated the effects of alcohol on cognitive ERPs in HR and LR subjects (Porjesz and Begleiter 1990). Twenty-four pairs of male HR and LR subjects (aged 19–24) received either a placebo or one of two ethanol doses (0.5 ml/kg and 0.8 ml/kg) mixed with three parts ginger ale on three separate occasions. A visual ERP paradigm involving easy and difficult line orientation discriminations was utilized. ERPs and measures of levels of intoxication were obtained pre-ethanol and at 20, 60, 90, and 130 minutes following ethanol ingestion. Blood alcohol levels (BALs) were monitored at 10-minute intervals throughout the test session.

No differences were obtained between groups in terms of BALs or intoxication ratings. The latency of P3 occurred significantly later to the difficult discrimination target than to the easy target in both groups of subjects. The high dose of alcohol significantly increased the latency of P3 to the difficult target in both groups of subjects. This effect was maximal between 60 and 90 minutes post-ethanol and was significant at all but occipital electrodes. There was a tendency for these alcohol-induced prolonged P3 latencies to recover to pre-alcohol ranges in the HR group. However, they remained delayed in the LR group throughout the study (130 min post-alcohol). In another study, Schuckit et al. (1988) report that FHP males recover more quickly from P3 latency delays induced by alcohol.

The N1 amplitude was significantly decreased by alcohol ingestion, particularly for the non-target stimulus at occipital leads. This result was more pronounced in the FHN than the FHP group. Although N1 amplitude to non-targets remained depressed in the FHN group throughout the test session, it recovered in amplitude by 90 minutes post-ethanol in the FHP group. These results suggest that the HR subjects exhibited more innate tolerance to alcohol than did the LR group. The N1 amplitude did not decrease to the difficult target and was somewhat decreased to the easy target by alcohol. These results support the finding by Roth et al. (1977) that attentional factors can counteract the N1 decreases caused by alcohol and the finding by Campbell and Lowick (1987) that the largest alcohol effects are obtained when attention is mobilized least (to non-targets). It was concluded that ERPs provide sensitive indices of state and trait variables involved in alcohol consumption and that different ERP characteristics are sensitive to different aspects of this multifaceted problem.

SUMMARY AND CONCLUSIONS

The foregoing review of the electrophysiological research in individuals at risk for alcoholism indicates that their ERPs can be characterized by low-voltage P3 amplitudes. This robust finding has been replicated in many different laboratories with different experimental paradigms. The low P3

amplitude is apparent in HR subjects without exposure to alcohol. Reduced P3 voltages have been reported in abstinent alcoholics and have not been found to recover with prolonged abstinence. In contrast, BAERs have been found to recover with prolonged abstinence in alcoholics, and do not differ between HR and LR subjects (Begleiter et al. 1987a). Taken together, this suggests that P3 deficits observed in alcoholics and HR subjects antecede alcoholism, whereas BAER abnormalities in alcoholics are the consequence of alcoholism.

There is substantial evidence indicating that electrophysiological characteristics (both EEG and ERP) are under genetic control. The P3 component has been reported to be more similar among monozygotic twin pairs than controls. In addition, ERPs have been reported to be similar in abstinent alcoholic fathers and their sons (Whipple et al. 1988). Thus, the reduced P3 voltage in HR subjects perhaps provides a phenotypic marker for alcoholism. However, it remains to be determined with longitudinal studies whether those HR individuals manifesting low P3 voltages are in fact those who go on to develop the disease of alcoholism.

HR and LR individuals have also been reported to differ in terms of other electrophysiological measures, namely, N2-P3a, MMN, and EEG. These findings, however, have not been replicated across different laboratories and may not be as robust as the P3 findings. Although it has been reported that HR subjects are characterized by excessive high-frequency EEG without the administration of alcohol, this has only been reported in one laboratory and has not been replicated even within the same laboratory.

In addition to electrophysiological measures that differentiate HR from LR individuals without exposure to alcohol, other electrophysiological measures have been reported to differentiate individuals at risk with the use of alcohol challenges (e.g., changes in alpha, recovery from N1 amplitude reductions, and P3 latency delays of the ERP). Although these electrophysiological measures could represent vulnerability markers for alcoholism, there has not been sufficient replication, and a substantial amount of disagreement remains in the literature.

The lack of consensus of results among laboratories can at least in part be attributed to differences in subject populations. The only definition of risk for alcoholism that these studies share is that at least the father must have been an alcoholic. Therefore, the density of alcoholism within the family fluctuates across studies. If only the individual's father and no other first- or second-degree relatives are alcoholic, this may not increase the genetic risk for alcoholism but may indicate a phenocopy or sporadic case. Furthermore, the clinical criteria for diagnosis of alcoholism in the father and the manner in which his alcoholism is assessed contribute to differences in the samples studied. Some studies require only one symptom of alcoholism in the father to

qualify for inclusion into the FHP group. Therefore the HR subjects in some studies may include offspring of heavy drinkers or problem drinkers. This dilutes the form of familial alcoholism, making it less likely to obtain significant results between groups. Problems such as comorbidity for other psychiatric problems are also treated differently in different studies; individuals manifesting comorbid psychiatric diagnoses (e.g., antisocial personality or affective disorder) may be excluded from some studies and included in others. Because alcoholism is a heterogeneous disease, HR groups in different studies may be composed of different numbers of offspring of different types of alcoholism (e.g., type 1 and type 2). Often the HR subjects studied are beyond the age of risk, or the stringent screening criteria rule out potential pre-alcoholics. Furthermore, environmental influences must be taken into account; variables such as socioeconomic status, education, and age may affect the results obtained. Additionally, differences in selection criteria for the control group may also determine whether differences between HR and LR groups will be found.

Various types of pre-alcoholics may manifest different electrophysiological patterns before and after alcohol administration. That alcoholism is a clinically heterogeneous disease with possible genetic heterogeneity is underscored by the fact that different studies often yield inconsistent results. Therefore, subject selection remains a major problem in HR research. Ideally, the HR sample should consist of young children without prior exposure to alcohol who are offspring of alcoholic fathers from families in which alcoholism is prevalent; these alcoholic fathers should be diagnosed directly, and other psychiatric disorders should be eliminated.

Electrophysiological measures have an advantage in that they can provide indices of both trait and state characteristics. These trait indices perhaps provide phenotypic markers (e.g., P3 amplitude, high-frequency beta) distinguishing subjects at risk for alcoholism without the administration of alcohol. The electrophysiological measures of state characteristics, namely, how an individual's EEG and ERP respond to alcohol (changes in alpha and N1 amplitude), also distinguish HR from LR groups, perhaps representing vulnerability markers for alcoholism. Furthermore, these electrophysiological measures may be useful in distinguishing different subgroups at risk for alcoholism. Future studies focusing on individual differences in electrophysiological measures before and after alcohol administration will help identify individuals at risk for specific types of alcoholism.

To determine whether these electrophysiological measures provide phenotypic markers of alcoholism, longitudinal studies will be needed to assess individuals as they pass through the age of risk. At present, there is no compelling evidence demonstrating that those individuals manifesting a low P3 amplitude are in fact destined to become alcoholics. Longitudinal family

studies are under way examining alcoholic and nonalcoholic families to determine which family members become alcoholic as they pass through the age of risk. It is hoped that this approach will elucidate the link between measures of risk and the development of alcoholism.

The foregoing review suggests that electrophysiological measures may serve as phenotypic markers for alcoholism. It is not suggested that these phenotypic markers are necessarily specific for alcoholism, nor is it suggested that all individuals manifesting these "markers" will necessarily go on to abuse alcohol. However, there is evidence that individuals at risk for alcoholism (sons of alcoholic fathers) can be distinguished from those not at risk for alcoholism with electrophysiological measures, both without the ingestion of alcohol and in response to alcohol challenges. Since these electrophysiological measures are genetically determined, the data imply that a predisposition or vulnerability to alcoholism is inherited. The role of environment and the gene-environment interaction are not to be minimized in determining whether an individual manifesting this predisposition goes on to abuse alcohol.

ACKNOWLEDGMENT

This work was supported by National Institute on Alcohol Abuse and Alcoholism grants AA-02686 and AA-05524.

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COMMENTS

Searles: I want to ask Henri about the differences between your findings and John Polich's findings.

Begleiter: The findings from our lab have been replicated in a few places, including our own lab, except in Polich's lab. I think the primary difference—and I'll let John disagree if he wishes—the primary, probably the sole, difference is on two levels. One is our subject selection; we are dealing with totally different subject groups. The subjects in John's lab are recruited in a similar manner to what Marc Schuckit does. That is, a questionnaire is sent out on the UCSD campus; they recruit a different kind of individual than we would. Selection criteria, ascertainment are really totally different. I believe that's the most important difference. The second difference, and probably less important, are tasks used, our paradigms. Our tests are all visual, with the exception of one. They are fairly demanding tasks, typically more demanding than what Polich has used. I would attribute the difference in our findings to these two factors.

Polich: I agree totally. Because of equipment limitations, I wasn't able to implement a lot of visual-type tasks at the time I did those studies. Then, as the field emerged, I became very sensitized to the difference, as Henri said, in terms of the differences in his population and mine, and also this task difference, which I really think plays a big part.

Reich: Henri, you've got the six dipoles at this point.

Begleiter: We have up to six dipoles.

Reich: Yes, and, assuming each dipole is a nucleus or a generator of some import, if you think of the brain as a collection of organs, there are probably a lot more. Is there any theoretical limit to the number of dipoles?

Begleiter: At this point, it's computer bound. However, remember, we are looking to fit data to a specific physiological event. We can be sure there aren't 10 million dipoles going on where that is generated. That's a well-known fact. How many there are, I can't be sure. Indeed, when you try to see the number of dipoles, you rarely have to exceed 6. You can optimize, again using a numerical procedure, using a simplex procedure, you can account for most of your data using 2 or 3 dipoles per derived component.

Reich: That may be the consequence of a small amount of information.

Lander: One question; what about girls? You're studying boys. Any naive model I have I should expect to see in girls or I'd like to know a good reason why it's not there.

Begleiter: We have never studied girls and probably are not going to, at least in the next couple of months, but there are people who have. The group at McLean Hospital has studied some females. Does anyone know what they find? I don't.

Schuckit: Dr. Lex replicates our kind of stuff, but she hasn't looked at the electrophysiology yet. They'll get to it, I'm sure.