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Chapter Nineteen

BRAIN ELECTROPHYSIOLOGY AND ALCOHOLISM

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Summary

The literature on the affects of chronic alcohol intake on brain evoked potentials (EP) in man is reviewed. These various EP techniques can assess the functional integrity of the brain, and are sensitive to the effects of alcohol tolerance, withdrawal and long-term brain dysfunction. Abstinent chronic alcoholics (≥ 3 weeks) show a number of abnormalities in these parameters, and these are described. Recent evidence indicates that P3 deficits in EP may antedate alcohol abuse: 35-40 per cent of sons of alcoholic fathers manifest low P3 amplitudes without prior exposure to alcohol.

In recent years it has become evident that chronic alcoholism is associated with a broad spectrum of brain disturbances ranging from the severe symptoms of the Wernicke-Korsakoff (1,2) to the more subtle, but nonetheless significant, cognitive disturbances characteristic of the majority of alcoholic patients. In some patients, the brain dysfunction may be a significant factor in their inability to abstain from alcohol.

The etiology of the development of alcohol-related brain damage or dysfunction is still ambiguous. There is increasing evidence that the ingestion of alcohol results in central nervous system (CNS) changes during intoxication and withdrawal and subsequent to chronic alcohol abuse. These CNS changes are quite long-lasting, and in fact, it is presently unclear whether complete recovery takes place with prolonged abstinence. While the brain is quite susceptible to the deleterious effects of alcohol, the exact consequences of alcohol or acetaldehyde toxicity and withdrawal phenomena on brain function, and their interaction

with repeated patterns of alcohol exposure are not known at the present time. The role of other possible contributing factors such as genetic factors, abnormal thiamine metabolism, nutrition and malabsorption, liver pathology, age of onset of alcoholism and possible premorbid brain dysfunction remains poorly understood.

The advent of computer technology has led to the development of sophisticated evoked brain potential techniques used to assess the functional integrity of various brain systems. The evoked potential (EP) or event-related (ERP) techniques offer a unique opportunity for assessing level of brain functioning. The quantitative analysis of salient EP features reflect various aspects of brain function related to sensory and integrative brain processes as well as the functional integrity of different neurophysiological systems. These powerful EP techniques represent the interface between cellular neurobiology and the behavioural sciences. Recording electrical activity from the brain has proved to be extremely sensitive to all the various CNS dynamics reflecting alcohol-related effects, namely: alcoholisation, tolerance, withdrawal and long-term brain dysfunction (3,4).

In recent years, a number of studies have demonstrated that acute administration of moderate to high alcohol doses depresses the electrical activity of the brain. These data have been reviewed for the electroencephalogram (5,6).

Numerous animal studies have shown that prolonged alcohol administration produces decrements in evoked potential amplitudes (7,8) and slowing in conduction velocity of the Brain-Stem Potential. These alcohol-related EP changes are attenuated when tolerance develops (8). The abrupt removal of alcohol produces a rebound CNS hyperexcitability characterised by increased EP voltages (7,9-11) and significantly shortened brainstem potential latencies (8). This central nervous system hyperexcitability has been found to persist long after clinically observable signs and symptoms of withdrawal have dissipated (3,7-10,12-14). This protracted subacute withdrawal syndrome has been studied in various animals including man and is typically characterised by hyperexcitability of the central nervous system.

The study of CNS dysfunction caused by the neurotoxic effects of chronic alcohol abuse may be obscured or totally masked by the CNS deficits manifested during the protracted subacute withdrawal syndrome. This problem is particularly critical in

the course of investigating possible recovery of function. If the initial assessment of CNS deficits occurs too soon after alcohol withdrawal, the study of reversibility will be confounded by the interaction of withdrawal-related deficits and the neurotoxic deficits caused by chronic alcohol abuse. Studies of brain deficits related to the long-term neurotoxic effects of alcohol can only be conducted in patients who have been totally abstinent and medication-free for a minimum of three to four weeks.

In our laboratory we recently recorded auditory brain stem potentials from alcoholics who were totally abstinent from alcohol for one month (15). We found that alcoholic patients manifested significant delays in latencies and brain stem transmission time between peaks II-V. Similar findings have been reported in neurologically impaired abstinent alcoholics (16). In an extensive study of chronic alcoholics, Chu et al. (17) reported that alcoholics with cerebellar degeneration had the highest incidence of abnormal brain stem potentials. Furthermore they found a high correlation between CAT-Scan abnormalities and brain stem transmission delays. They report a progressive increase in the incidence of abnormal brain stem potentials with age and the number of alcoholic neurological symptoms. We (15) have postulated that the increase in neural transmission time may reflect the process of demyelination which has been suspected in chronic alcoholics (18) and has been observed in rats chronically exposed to alcohol (19). While the delays in brain stem transmission time may be caused by the neurotoxic effects of alcohol, it is possible that nutritional deficiences in and of themselves produce demyelination resulting in brain stem delays. Nutritional deficits are known to lead to such demyelinating diseases as polyneuropathy, and central pontine melinolysis. Preliminary data from our laboratory suggest that alcoholics with signs of nutritional deficits and/or polyneuropathy display a different BSP waveform than other alcoholics. It is quite possible that the interaction of factors such as length of drinking history, amount consumed per sitting, number and severity of withdrawal episodes and nutritional status may be the critical determinants of brain stem abnormalities in chronic alcoholics. We are currently investigating whether these BSP aberrations are reversible following four months of abstinence in the same patients. Our preliminary results indicate that following four months of total abstinence,

despite marked improvements in central conduction times for peaks III-V in the same patients, neural conduction velocities still remain significantly slower than those obtained in control subjects.

For the past several years in our laboratory, we have systematically examined neurophysiological concomitants of cognitive deficits in abstinent medication-free alcoholics, using event-related brain potentials. With the use of a bimodal (visual and auditory) paradigm we investigated the ability of alcoholics to focus on a relevant stimulus modality while inhibiting responding to an irrelevant modality. We studied the NI component of the ERP (20). The NI component is sensitive to the selection of a relevant or irrelevant stimulus modality; in normal subjects, the NI component is enhanced to all stimuli in a relevant channel, and typically depressed to stimuli in irrelevant channels.

The results indicated that abstinent alcoholics manifested abnormally reduced NI voltages, particularly over the right hemisphere frontal and central loci. Furthermore we found that less hemispheric asymmetry was evident in the alcoholic patients than in the control subjects. These findings are remarkably similar to the results obtained with acute doses of alcohol in healthy subjects (21-23). This suggests that the brain dysfunction in chronic alcoholics resembles aberration detected in normal individuals under the influence of alcohol.

The advantage of using an information-processing ERP design to assess brain functioning is that it provides additional information comparing responses to identical relevant and irrelevant inputs. Indeed, we found that in contrast to healthy subjects, the amplitude of NI remained the same in the alcoholics, regardless of whether the stimulus was in the relevant or irrelevant modality. This suggests that chronic alcoholics may be incapable of appropriate "sensory filtering".

In another series of experiments in our laboratory, we investigated brain dysfunction in chronic alcoholics with the P3 component using a visual-stimulus selection ERP paradigm (24). ERP's were obtained to targets (rarely occurring, task relevant geometric shapes) non-targets (frequently occurring task-irrelevant random shapes) stimuli. The subject's task was to press a button only to the target stimulus. In this study, all stimuli were in the relevant channel and were expected to have enhanced NI components. However, the P3 component

could only be obtained to rarely occurring stimuli that were either task-relevant (targets) or irrelevant (novels). Thus, the experimental design tests their ability to probability-match stimuli in terms of their frequency of occurrence. Target and non-target stimuli were alternated every other block so that ERP's could be compared to the same stimulus when it served as a target and non-target.

As in our bimodal experiment (20), we found that the NI component amplitude was significantly depressed in alcoholics to all stimuli (targets, non-targets, novels), to levels comparable to an irrelevant stimulus modality, despite the fact that all stimuli were in the relevant modality. Taken together, on the basis of the NI data, these studies suggest that "sensory filtering" processes are impaired in chronic alcoholics.

Furthermore, we found that P3 amplitudes were significantly depressed or absent in alcoholic patients to rare target stimuli under conditions optimal for eliciting a large P3 component. This finding was most pronounced over parietal areas where P3 amplitudes are maximal at scalp (25-27). While normal controls manifested differentially enhanced P3 components to target stimuli, alcoholics manifested identical low amplitude P3 components regardless of whether a stimulus was a target or non-target. Thus the major ERP aberration manifested by chronic alcoholics is the lack of differentiation between their responses to relevant and irrelevant inputs and the low voltages of their event-related activity.

The P3 component has been considered a manifestation of the orientating response (25,28-30). More recently it has been suggested (31) that the P3 component indexes the motivational properties or value of stimuli. There is good evidence that the P3 component derives, in part, from subcortical sources. Wood et al. (32) conducted intracranial studies in humans and suggested that the P3 was generated by subcortical structures. Halgren et al. (33) used auditory and visual P3 paradigms while recording scalp and intracranial potentials in humans. They recorded a large P3 component to the significant stimuli and concluded that the P3 component was generated in the hippocampus and amygdala. The direct demonstration of a limbic system contribution to the scalp-recorded P3 is in accord with this system's role integrating drive-related behaviour. In this regard it is interesting to note that the P3 amplitude is quite low in patients with

aberrant levels of motivation (31). Moreover, if P3 indexes the subjective motivational properties of stimuli, it is reasonable to assume that events which elicit a P3 will be remembered better than those events which do not elicit a P3. This is illustrated with some preliminary data (30,34) which indicates that there is a relationship between the amplitude of P3 and the memorability of the eliciting stimuli. This relationship is further supported by the fact that structures (hippocampus and amygdala) which are in part responsible for the production of P3 are also directly involved in memory processes (35).

Thus our results that chronic alcoholics manifest low-voltage or even absent P3 components under conditions designed to elicit maximum P3 component amplitudes may be indicative of deficits in limbic system (hippocampus-amygdala). The involvement of the hippocampus in chronic alcohol intake has recently been demonstrated in neuropathological (36-38) and electrophysiological studies (13) with animals. On the basis of several ERP studies in our laboratory (6) we conclude that alcoholics have difficulty evaluating the potential significance of a stimuli. They do not neurophysiologically differentiate between relevant and irrelevant stimuli, but rather maintain the same ERP characteristics regardless of the task requirements. This perhaps indicates that their template for match/mismatch decisions is lost or not readily available. This suggests memory deficits at the encoding level where each incoming stimulus must be evaluated anew.

Recent evidence from our laboratory indicates that while BSP aberrations improve with prolonged sobriety, P3 deficits do not (39). While it has generally been assumed that brain abnormalities observed in alcoholics are due to the toxic effects of alcohol on the brain, nutritional deficits or an interaction of alcohol and nutritional-related factors, the etiology of these brain abnormalities is still unknown. The possibility that these brain deficits may in fact precede alcohol abuse has only been suggested very recently. There is increasing evidence that certain individuals are at high risk for developing alcoholism. Specifically, sons of alcoholic fathers are four times more likely to become alcoholics than sons of non-alcoholic fathers (40) even when separated from their biological parents soon after birth. A number of elegant studies of male adoptees indicate that the biological rather than the adoptive parent is predictive of

later alcohol abuse in the adoptee (41-46). Taken together, these studies suggest that a genetic factor predisposing sons of alcoholics to alcoholism may be involved.

The identification of a suitable biological marker (or markers) that is genetically transmitted would be necessary to provide more definitive evidence that the etiology of alcoholism involves genetic factors. It is very likely that some brain pathophysiology may be involved in the biological predisposition for alcoholism. There is already good evidence to indicate that brain EP waveforms are genetically determined (47). Recently it has been demonstrated that the effects of alcohol on the electroencephalogram (48,49) and on the event-related brain potentials (50) are genetically determined.

We have recently undertaken an investigation of the possibility that sons of alcoholic fathers manifest brain anomalies that antecede any exposure to alcohol. We have recorded ERP's in boys between the ages of six and fourteen, comparing electrophysiological recordings from sons of alcoholic fathers (high risk) and age and education-matched sons of non-alcoholic parents (low-risk). Children with mothers who drank alcohol during pregnancy are excluded. Boys are excluded if they have had any experience with alcohol or illicit drugs. Our preliminary findings are quite striking. In one neurophysiological study (51) we found that the P3 component and slow wave of ERP's obtained from high risk subjects was significantly lower in amplitude than those found in control subjects. Not all high risk subjects manifested neurophysiological deficits in the ERP. However, it should be noted that the group ERP waveforms were remarkably similar to ERP waveforms recorded in adult alcoholics; whether these ERP aberrations are in fact markers for a predisposition to alcoholism remains to be tested. We are testing the children in our samples periodically to determine whether individuals manifesting ERP anomalies are in fact the ones who develop problems with alcohol.

In keeping with our findings, it is important to note that a group of researchers at the Salk Institute (50) has recently found that adult males with a family history of alcoholism respond differently to challenge doses of alcohol than matched controls. Individuals with a family history of alcoholism showed a signigicant P3 amplitude reduction and an increase in P3 latency in response to alcohol as compared to matched subjects. Taken together,

results in young children at high risk from our laboratory and those in adults at the Salk Institute suggest that individuals with a family history of alcoholism tend to manifest different ERP waveforms than those without a family history of alcoholism. It remains for future research to separate those brain aberrations that antecede alcohol abuse from those that are the consequence of years of alcohol abuse. It is not known at the present time which innate differences determine responsiveness to alcohol predisposition to alcohol abuse.

While the aforementioned findings in high risk subjects are preliminary, the data obtained thus far are sufficiently encouraging to entertain the possibility that specific brain dysfunctions may be considered tentative biological markers which antecede the onset of alcoholism. If these data prove to be valid and reliable, we may begin to devote some of our efforts to the identification of subjects at risk for alcoholism, and consequently, to design and initiate prevention procedures to help remedy a severe disease which affects much of our nation.

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Chapter Twenty

THE FETAL ALCOHOL SYNDROME

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Summary

It is safe to conclude from the literature that alcohol abuse during pregnancy is associated with increased risk for poor pregnancy outcome in both man and animals. The mechanism of action, however, is not known. Possible mechanisms of action which would be amenable to pharmacotherapy are discussed. These include nutritional variables, impaired placental transport, fetal hypoxia, direct embryotoxicity, and acetaldehyde-induced damage. Pharmacologic agents could be produced to mitigate these effects of ethanol and, perhaps, decrease the incidence and/or severity of FAS.

The physical and mental inferiority of children born to alcoholic parents has been recognised for several hundred years (1,2). However, the teratogenic potential of ethanol, as separate from genetic damage, was not realised until relatively recently. Two independent groups, one in France (3) and one in the United States (4) identified a common pattern of birth defects in offspring of alcoholic mothers who abused alcohol throughout pregnancy. The constellation of anomalies was termed Fetal Alcohol Syndrome (FAS) by Jones and his colleagues (4) in 1973. Several hundred clinical and animal reports have appeared in the literature within the last ten years confirming the teratogenicity of alcohol and the existence of FAS around the world (5). Even the most skeptical clinician or layman must be swayed by this voluminous literature.

It appears safe to conclude from the available data that alcohol abuse during pregnancy is associated with increased risk for poor pregnancy outcome. Risks include more frequent spontaneous abortions (6,7,8), as well as offspring with FAS characterised