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PERSISTENCE OF A "SUBACUTE WITHDRAWAL SYNDROME" FOLLOWING CHRONIC ETHANOL INTAKE

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The critical determinants in the development of alcohol addiction are unknown, and the specific nature of the addictive process remains a matter of conjecture. In recent years, however, a number of investigators have succeeded in producing physical dependence on alcohol in different animal species. These various studies have been thoroughly reviewed [1 - 3]. Comprehensive behavioral rating scales for signs of physical dependence have been developed for the mouse [4, 5], for the rat [6], for monkeys [7], and for man [8]. While there has been considerable progress in developing quantitative behavioral techniques for the assessment of withdrawal, there have been few systematic attempts to examine the physiological correlates of withdrawal from ethanol.

As the grossly observable behavioral signs of withdrawal presumably reflect central nervous system (CNS) hyperexcitability, a number of electroencephalographic studies have been conducted in humans and have been reviewed by Begleiter and Platz [9]. Since that review of the literature, a number of investigators have used the promising technique of recording evoked brain potentials from scalps of alcoholic patients. In 1974, Begleiter *et al.* used the recovery function of somatosensory evoked potentials to examine changes in brain excitability of alcoholics during withdrawal from alcohol [10]. A recovery function was determined every morning (ten hours after the last drink), during three days of baseline, four days of alcoholization, and the four days subsequent to withdrawal from alcohol. The findings indicated a progressive increase of brain excitability starting approximately ten hours after the last drink and reaching asymptote with the first day of total alcohol withdrawal. These results support the hypothesis of increased CNS excitability during withdrawal, and strongly indicate that the degree of CNS hyperexcitability increased with each additional day of alcohol intake. Our findings of increased voltages in the late components of the evoked brain potentials in man following withdrawal have been confirmed by Jarvilehto *et al.* [11], Coger *et al.* [12], Wagman *et al.* [13], Lelord *et al.* [14], and Pfefferbaum and Roth [15].

Coger *et al.* [12] found that alcoholics in withdrawal manifested higher visual evoked potential voltage (P100–N140 component) than normal. In addition, they reported that alcoholics who had been abstinent from alcohol for three to four weeks also exhibited electrophysiological hyperexcitability.

Similar findings were obtained by Wagman *et al.* [13], who found that some alcoholics, detoxified for 7 - 21 days, manifested increased amplitudes of visual evoked potentials. More recently, Pfefferbaum and Roth [15] reported increased P3 amplitudes to auditory stimuli presented to chronic alcoholics abstinent for a period of three weeks. Lelord *et al.* [14] were able to demonstrate that alcoholics abstinent from alcohol for ten days were more responsive to phantom light than normal controls. The incidence of emitted potentials was higher in alcoholics than in normals. The authors concluded that these findings are indicative of CNS hyperexcitability and attributed this to a deficit in cortical inhibitory mechanisms.

For the past several years, in our laboratory, we have systematically studied the electrophysiological concomitants of withdrawal following the cessation of chronic alcohol intake in animals. Begleiter and Coltrera [16] reported that withdrawal from ethanol subsequent to chronic intake resulted in changes in evoked brain potentials suggestive of CNS hyperexcitability. Furthermore, it was reported that these electrophysiological indices reflected hyperexcitability lasting for a period of at least 24 hours subsequent to withdrawal from ethanol. In a subsequent experiment, Porjesz *et al.* [17] found that the neurophysiological responses of post-addicted rats to challenge doses of alcohol were readily distinguishable from those of naive animals. More recently, Begleiter and Porjesz [18] examined the persistence of brain hyperexcitability following chronic alcohol exposure in rats. Evoked potentials were recorded from implanted electrodes in experimental (alcohol) and control (water) rats. The experimental rats were intubated daily for 14 days with progressively increasing quantities of 20% alcohol (3 - 8 g/kg), while the control animals received an equivalent amount of water in the same fashion. Beginning 4.5 hours after the last dose of alcohol via intubation, visual evoked potentials were sampled every half-hour up to eight hours, and again 24 - 27 hours after withdrawal. All experimental animals manifested their greatest brain hyperexcitability seven to eight hours after alcohol withdrawal. Following two weeks of abstinence, half of the experimental rats and half of the controls received an alcohol challenge dose (2 g/kg, intraperitoneally), while the remaining animals received the same challenge dose after five weeks. The results indicated that rats previously exposed to alcohol for a period of two weeks show a substantial increase in CNS hyperexcitability during the period of withdrawal. These findings are quite consistent with our previous data and are in full agreement with findings of other investigators using behavioral indices of withdrawal.

These findings indicate that a state of CNS hyperexcitability persists long after the removal of alcohol. These CNS changes appear to be long-lasting and can best be observed subsequent to the administration of a challenge dose of alcohol. In additional experiments from our laboratory [19], we have observed a significant relationship between the length of exposure to, and quantity of, alcohol and the persistence of these CNS aberrations.

More recently we conducted electrophysiological studies in monkeys (*Macacca radiata*) to determine which specific brain sites are involved in the

persistence of this neural hyperexcitability [20]. Experimental and control animals were implanted with recording electrodes located at various brain sites. Experimental animals were intubated daily with 25% ethanol (5 g/kg) for a period of 30 days, while the control animals were intubated with an equivalent amount of isocaloric sucrose. Both groups were also intubated with 2.0 ml of Poly-vi-sol multiple vitamin drops every other day through the 30-day period. Evoked brain potentials were recorded in all animals 20 minutes prior to intubation (baseline). Recordings were also taken following the last day of intubation (every 20 minutes for the first two hours, and every hour thereafter for 22 hours). During the next 37 days, the animals were maintained under standard laboratory conditions. After 37 days, evoked potentials were again recorded from all animals. Twenty minutes later all monkeys were intubated with a challenge dose of alcohol (2.0 g/kg, 25% solution), and evoked potentials were recorded for a 24-hour period as explained before.

The results of this study indicate that in the monkey, ethanol withdrawal is accompanied by increases in the late component of the visual evoked potential. These electrophysiological changes reflect significant increases in neural hyperexcitability and are quite consistent with our data obtained in humans and those observed in rats.

It should be noted that this neural hyperexcitability may be localized in specific brain sites. Our results in the monkey experiment indicate that significant changes in hyperexcitability were obtained at mesencephalic reticular formation, hippocampus, frontal cortex, and posterior association cortex. At other sites, such as supraoptic nuclei, visual cortex and lateral geniculate body, we did not observe any increase in hyperexcitability for 24 hours following a challenge dose of alcohol. It is quite obvious that the electrophysiological responses of the experimental animals are quite different from those of the control animals after the administration of a challenge dose of alcohol. The experimental animals manifest a state of neural hyperexcitability which persists for several hours, depending on the specific brain site. Taken together, these data indicate that a state of latent hyperexcitability persists long after the removal of ethanol. This neural hyperexcitability is present in the absence of gross convulsive behavior and is manifested selectively in different areas of the CNS subsequent to a challenge dose of alcohol. This latent CNS hyperexcitability may well be considered part of a protracted subacute withdrawal syndrome, which readily becomes reactivated by re-exposure to ethanol.

Our findings suggest that physical dependence involves CNS alterations which persist for long periods of time subsequent to the administration and removal of ethanol. Until recent years, these alterations were quite unspecified and not readily amenable to laboratory investigations. However, in the last few years, several investigators have been able to isolate and study a wide spectrum of physiological disturbances which are long-lasting and may be taken to reflect residual symptomatology of the withdrawal syndrome. These long-lasting physiological disturbances may be considered to be a form

of memory. The time course of development, duration and mechanisms of such an agent-induced "addiction memory" are at present unknown.

It is quite plausible that the residual withdrawal syndrome may in some way contribute to an increased risk of returning to alcohol use [21, 22]. Recently DeNoble and Begleiter [23] studied the effects of prior alcohol exposure on alcohol self-administration in monkeys. We reported that previously exposed animals self-injected significantly more alcohol during the first two alcohol test days than naive animals did; thereafter, the self-injection rates of the two groups were approximately the same. It should be noted that the prior exposure of our animals to alcohol occurred four months before the beginning of the experiment. In general, these data suggest that long-term CNS changes caused by chronic exposure to alcohol may be more critical in the susceptibility of the ex-addicted organism to re-addiction rather than in the determination of the total volume consumed over time.

It is quite encouraging to note that a highly objective and quantifiable electrophysiological measure such as evoked brain potentials can be used as a direct index of neural activity in three different species, namely the rat, monkey and man. It is most interesting to realize the striking similarities in neural hyperexcitability manifested in these three species in response to withdrawal from chronic ethanol intake. If we are to develop a meaningful animal analogue of the human withdrawal phenomenon, it is imperative that we use direct objective and quantifiable measures to assess the basic withdrawal aberrations common to several species, including man.

A similar methodological plea must naturally be made for the study of tolerance. It is rather common for investigators interested in the relationship between tolerance and physical dependence to use different dependent variables to assess tolerance and physical dependence. This practice is very much responsible for the divergent results in this area of research. To date there has been no attempt to achieve uniformity of techniques for assessing tolerance and physical dependence. The measurement of tolerance and physical dependence is commonly achieved with the use of gross behavioral measures which are often subject to extraneous influences not at all related to the effects of alcohol. To choose one technique to measure tolerance and another to assess physical dependence will continue to produce incomprehensible findings. The choice of several appropriate dependent variables will not only help us to understand better the relationship between tolerance and physical dependence, but, more important, it will very likely result in a more meaningful understanding and use of ambiguous concepts such as "tolerance" and "physical dependence".

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