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Does Acetaldehyde Play a Role in Alcoholism?

Behavioral versus Biochemical Analysis

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1. INTRODUCTION

The issue whether acetaldehyde plays a functional role in the actions of alcohol remains a controversial area following more than two decades of investigation. The publication of several extensive reviews (Lindros, 1978; Amir et al., 1980; von Wartburg, 1980; Brien and Loomis, 1983, Amit and Smith, 1989) have left little doubt that the first metabolic product of alcohol oxidation is an important contributor to some of the consequences of exposure to ethanol. Unfortunately, despite the massive literature that accumulated during this period, there is, as yet, little consensus concerning which actions of alcohol (if any) are a function of the formation of acetaldehyde.

This chapter therefore reviews and evaluates the behavioral and psychopharmacological data on the possible role of acetaldehyde in the actions of alcohol. Furthermore, we have based the argument on the contention that the positive reinforcing properties of alcohol are the primary variables underlying the development of dependence on alcohol. It follows logically that any suggestion that acetaldehyde may play a role in alcoholism must incorporate within its framework evidence supporting the involvement of acetaldehyde in those reinforcing and dependence-producing properties of alcohol. This chapter was written as an attempt to do so. Finally, we have attempted to evaluate the relevance of primarily negative biochemical data and contrast it with the significance of a growing body of behavioral data supportive of this notion.

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2. ACETALDEHYDE AS A TOXIC SUBSTANCE

Traditionally, acetaldehyde has been viewed as a toxic by-product of ethanol metabolism (Hald and Jacobsen, 1948; Jacobsen, 1952). It is known, for example, that prolonged ethanol exposure may disrupt liver function (Hasumura et al., 1975). It was perhaps because of these earlier observations that acetaldehyde's aversive effects have initially drawn the greatest attention. The apparent toxicity of peripheral accumulation of acetaldehyde has in fact served as the basis of a treatment model for alcoholism (Ritchie, 1970; Sellers et al., 1981). This presumably toxic elevation in blood concentration of acetaldehyde was brought about through the use of pharmacological agents that are capable of inhibiting hepatic aldehyde dehydrogenase (ALDH). Two such agents widely used in the treatment of alcoholism are disulfiram (Antabuse) and the cyanamide derivative calcium carbimide (Temposil) (Ritchie, 1970; Sellers et al., 1981). In the presence of alcohol, these agents induce a reaction known as the disulfiram–alcohol reaction. Manifestations of this interaction include vasodilatation, tachycardia, decreased blood pressure, dizziness, nausea, and vomiting (Kitson, 1977; Truitt and Walsh, 1971). In more severe cases, respiratory depression, cardiovascular collapse, and death may occur (Jacobsen, 1952).

It had long been thought that the elevation of acetaldehyde levels via the use of these agents served to limit alcohol drinking (Eriksson, 1980*a*; Lindros et al., 1975; Schlesinger et al., 1966; Sellers et al., 1981). It was demonstrated in both humans as well as laboratory animals (although exceptions were, in fact, reported) that administration of disulfiram or cyanamide reduced voluntary consumption of ethanol (see Lindros, 1978). This notion has been supported by investigations of the innate alcohol sensitivity observed in some Orientals (Goedde et al., 1979; Mizoi et al., 1983; Wolff, 1972). These studies revealed that approximately 50% of Japanese lack the hepatic mitochondrial low K_m isozyme of ALDH (Harada et al., 1980; Mizoi et al., 1983). Ingestion of low to moderate doses of alcohol in these individuals results in much higher blood acetaldehyde levels than that found in Caucasians after ingestion of similar amounts of alcohol. Because of the inability to metabolize acetaldehyde quickly and efficiently, these Orientals have a heightened sensitivity to alcohol and experience dysphoric reactions (Goedde et al., 1979; Mizoi et al., 1979). This reaction is similar to that observed in alcoholics who consume alcohol while receiving disulfiram or calcium carbimide (Brien and Loomis, 1983; Tottmar et al., 1977). In a study conducted by Harada et al. (1983), approximately 40% of healthy Japanese males sampled displayed a deficiency in the low K_m isozyme of ALDH; however, only 2.3% of Japanese alcoholics were in this group, suggesting that the deficiency of this isozyme of ALDH in Orientals may be a genetic factor protecting this subpopulation from excessive alcohol intake and the subsequent development of alcoholism.

3. ACETALDEHYDE AS A REWARDING AGENT

The foregoing seems to support the view that the effects of acetaldehyde were primarily aversive in nature; however, clinical evidence and more recent experimental data suggest that this may not be the case in every instance. There can be no question that high concentrations of acetaldehyde circulating in blood have aversive conse-