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The role of acetaldehyde in the neurobehavioral effects of ethanol: A comprehensive review of animal studies

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Abstract

Acetaldehyde has long been suggested to be involved in a number of ethanol's pharmacological and behavioral effects, such as its reinforcing, aversive, sedative, amnesic and stimulant properties. However, the role of acetaldehyde in ethanol's effects has been an extremely controversial topic during the past two decades. Opinions ranged from those virtually denying any role for acetaldehyde in ethanol's effects to those who claimed that alcoholism is in fact ''acetaldehydism''. Considering the possible key role of acetaldehyde in alcohol addiction, it is critical to clarify the respective functions of acetaldehyde and ethanol molecules in the pharmacological and behavioral effects of alcohol consumption. In the present paper, we review the animal studies reporting evidence that acetaldehyde is involved in the pharmacological and behavioral effects of ethanol. A number of studies demonstrated that acetaldehyde administration induces a range of behavioral effects. Other pharmacological studies indicated that acetaldehyde might be critically involved in several effects of ethanol consumption, including its reinforcing consequences. However, conflicting evidence has also been published. Furthermore, it remains to be shown whether pharmacologically relevant concentrations of acetaldehyde are achieved in the brain after alcohol consumption in order to induce significant effects. Finally, we review current evidence about the central mechanisms of action of acetaldehyde.

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Abbreviations: 4-MP, 4-methylpyrazole; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; AT, 3-amino-1,2,4-triazole; BBB, blood–brain barrier; CTA, conditioned taste aversion; CYP2E1, cytochrome P4502E1; H_2O_2, hydrogen peroxide; LTP, long term potentiation; THBC, tetrahydro-β-carboline; TIQ, tetrahydroisoquinoline; VTA, ventral tegmental area

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1. Introduction

Alcohol abuse is an acute health problem throughout the world. Its consumption is linked to the occurrence of many pathological conditions, such as various forms of cancer, liver diseases, brain damages and fetal injuries during pregnancy. It is well established that acetaldehyde, the first product of ethanol metabolism, plays a key role in the toxic effects of ethanol, and most of the studies on ethanol metabolism were aimed at unraveling the effects of acetaldehyde in those pathological conditions. However, acetaldehyde has also been identified as a potential psychoactive drug that induces a range of behavioral effects. In particular, acetaldehyde is postulated to exert rewarding effects, at least in rodents. Such findings led to the idea that acetaldehyde might play a role in the pharmacological and behavioral properties of ethanol and especially in the development of alcoholism (Quertemont, 2004). In the field of alcohol research, the role of acetaldehyde in the central effects of ethanol has been a controversial issue for more than two decades. For some researchers, acetaldehyde is a key mediator of ethanol's neuropharmacological and behavioral effects. According to the most radical version of this theory, ethanol would be a mere pro-drug whose effects are fully mediated by its first metabolite, acetaldehyde. It has even been suggested that alcoholism might be renamed acetaldehydism (Raskin, 1975; Truitt and Walsh, 1971). On the opposite side, other alcohol researchers deny any role for acetaldehyde in ethanol's central effects (see discussion in Deitrich, 2004). They generally object that brain acetaldehyde concentrations after ethanol administration are far too low to induce any detectable pharmacological or behavioral effect. As it is the case in most scientific controversies, the truth is probably somewhere between these two extreme positions. The aim of the present review is to synthesize the current knowledge about the role of acetaldehyde in the central effects of ethanol. In the recent years, a number of animal studies have been published on that issue and there has been a renewed interest about the role of acetaldehyde in the central effects of ethanol. It is therefore timely to summarize the recent advances in the study of the role of acetaldehyde in the central effects of ethanol.

2. Historical background

The study of the involvement of acetaldehyde in ethanol's effects has already a long history. In the late forties, acetaldehyde was mainly studied for its toxic and adverse effects, especially in relation to the use of disulfiram in the treatment of alcoholics (e.g Martensen-Larsen, 1948; Glud, 1949). However, the suggestion that acetaldehyde might be involved in ethanol's behavioral and pharmacological effects also goes back to the late forties (e.g. Carpenter and MacLeod, 1952; Stoltz et al., 1944), although systematic investigations really started in the seventies. In that decade, a number of studies investigated the role of acetaldehyde in several behavioral and neurochemical effects of ethanol in both rats and mice (Amit et al., 1977; Brown et al., 1979; Dudek and Fuller, 1978; Holtzman and Schneider, 1974; Ortiz et al., 1974; Rydberg and Neru, 1972; Svensson and Waldeck, 1973; Truitt and Walsh, 1971), although their results were inconsistent. Some of these studies concluded that acetaldehyde plays a substantial role (Brown et al., 1979; Ortiz et al., 1974; Truitt and Walsh, 1971), whereas others indicated that acetaldehyde is not necessary for ethanol's effects to occur (Rydberg and Neru, 1972; Svensson and Waldeck, 1973). Some theories also ascribed an important role to acetaldehyde in the induction of alcohol dependence and alcoholism through its condensation with monoamines and their metabolites (Cohen and Collins, 1970; Davis and Walsh, 1970a; Walsh et al., 1970). Since such theories required pharmacologically significant acetaldehyde concentrations, efforts were made to measure blood and brain acetaldehyde levels after ethanol administration. Initial studies reported substantial concentrations of acetaldehyde in both the blood