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Review

Increased ethanol intake after prenatal ethanol exposure: Studies with animals

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Abstract

This review analyses the most relevant studies in which ethanol intake was measured after prenatal exposure to the drug. Despite the variety in methodology, in most such studies this prenatal experience induced a higher consumption of ethanol. Several variables that may affect the expression of this phenomenon are discussed, such as gender, age at testing, period of ethanol exposure, ethanol dose and conditions during the test. The mechanisms proposed in all these studies to explain the increased ethanol intake effect are also discussed. Some of these mechanisms are related to the teratological effects of the drug on the neurochemical systems involved in the reinforcing effects of abuse drugs, as well as on the regulatory systems of stress response. Another explanation of this phenomenon is also proposed in terms of associative learning. Specifically, the increased ethanol intake effect may be the result of a conditioned preference for ethanol acquired by the fetus when exposed to the drug during the last days of gestation.

Keywords: Prenatal ethanol exposure; Ethanol preference; Intake; Teratological effects; Rodents; Associative learning

Contents

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1. Introduction

In the early 1970s, results of clinical studies suggested an increased prevalence of alcoholism among the parents of hyperactive children, as well as higher rates of adult alcohol abuse in subjects who suffered from hyperactivity disorders during infancy (Cantwell, 1972; Goodwin et al., 1975; Morrison and Stewart, 1971). Most of these studies pointed to a genetic transmission of these "psychiatric disorders", although the possible role of environmental factors such as alcohol exposure during gestation was also considered (Morrison and Stewart, 1971, 1973). Due to the difficulties involved in clinical studies as regards isolating and analyzing interactions between all the factors involved in the effects of prenatal ethanol exposure, studies with laboratory animals acquired a special relevance. In particular, all those studies focusing on the effects of prenatal alcohol exposure on the offspring's alcohol consumption are of special interest for this review. The first relevant study using animals, published by Bond and DiGiusto (1976), reported that the progeny of pregnant rats administered with ethanol throughout pregnancy displayed greater activity and consumed significantly more ethanol than control offspring. These results, together with those obtained from clinical studies, raised the question of whether it was hyperactivity that predisposed subjects to alcohol abuse, or prenatal alcohol exposure which predisposed them to both alcoholism and hyperactivity (Bond and DiGiusto, 1976). Although the results of this first study with rats did not dismiss the interaction of genetic, social or family factors on increased ethanol intake and hyperactivity, it clearly highlighted the significance of the effects of alcohol exposure during fetal development. Since this first study by Bond and DiGiusto (1976), and during the 1980s, several other researchers have studied the increased ethanol intake effect after maternal ethanol ingestion from a teratological perspective. During the last decade, another set of studies have analyzed this effect focusing on what the fetus learns about ethanol when exposed to the drug.

Table 1 summarizes all studies analyzing the effects of maternal ethanol intake during gestation on offspring's ethanol consumption, among other indexes. Except for four studies in which no effects were reported, in all of them prenatal ethanol exposure increased ethanol intake in the offspring. This effect was observed with different strains of rats and also, in one study, with mice; with exposure to ethanol solutions, wine or beer; during short and long periods of gestation; and when subjects were evaluated during infancy, adolescence and adulthood. Despite the methodological differences between all these studies, several conclusions can be drawn regarding the factors mediating the increased ethanol intake effect.

2. Analysis of studies reporting increased ethanol intake after prenatal exposure

2.1. Period of exposure

Firstly, most of these studies seem to indicate that ethanol exposure exclusively during gestation is enough to induce an increased intake of ethanol (Arias and Chotro, 2005a, b; Bond and DiGiusto, 1976; Chotro and Arias, 2003; Dominguez et al., 1998; Hilakivi, 1986; Hilakivi et al., 1987; Holloway and Tapp, 1978; Lancaster and Spiegel, 1989; Molina et al., 1995, 1987; Nash et al., 1984; Nelson et al., 1983; Randall et al., 1983). In those studies in which ethanol exposure continued after birth, during lactation, the effect was still observed (Buckalew, 1979; Phillips and Stainbrook, 1976) and in some cases enhanced (Holloway and Tapp, 1978). These results corroborate those of a recent longitudinal clinical study which found a clear relationship between prenatal exposure to moderate ethanol doses and alcohol abuse related problems in 14-year-old adolescents (Baer et al., 1998) and in 21-year-old young adults (Baer et al., 2003). These studies found that ethanol exposure during intrauterine life is a better predictor of problems related to the drug than other factors such as a family history of alcoholism, nicotine exposure or other environmental variables such as parental consumption of other drugs (Baer, et al., 2003).

Is there a gestational period that is more sensitive to the effects of ethanol exposure on subsequent ethanol intake? Of those studies in which ethanol was administered only during pregnancy, the ones that could help answer this question are those in which dams were exposed during a restricted period of pregnancy. In general, ethanol exposure during the last two weeks of gestation seems to be enough to induce this increased ethanol intake effect. However, two periods can be identified in the rat from the results of the afore-mentioned studies. One is gestational day 8 (GD 8), on which the administration of two ethanol doses to the pregnant dam seem to be enough to increase ethanol intake in adult rats (Molina et al., 1987). In this case, the effect appears to be related to the process of gastrulation, an embryonic stage very susceptible to the physical teratological effects of ethanol (Sulik and Johnston, 1983). The other period that seems to be critical when observing this effect is the one identified in those studies in which low or moderate doses of ethanol were administered during the last days of gestation (GD 17–20) (Arias and Chotro, 2005a, b; Chotro and Arias, 2003; Dominguez et al., 1998; Molina et al., 1995). In this case, fetuses are exposed not only to the toxic effects of ethanol but also to the chemosensory aspects of the drug (Dominguez et al., 1996), which seems to be enough to induce a consistent increase in ethanol intake during the infantile and adolescent stages.

2.2. Ethanol dose and route of administration

Is there a threshold in the amount of ethanol needed for observing an increased ethanol intake effect? Although a considerable variety of ethanol doses were employed in all these studies, in general, they were relatively moderate to low amounts. For example, the increased ethanol intake effect was observed after only four i.g. administrations of 1 g/kg ethanol (Arias and Chotro, 2005b; Chotro and Arias, 2003; Dominguez et al., 1998) but also after maternal daily