Neurotoxicology and Teratology 41 (2014) 43–50

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Protective effects of the alcohol dehydrogenase-*ADH1B*3* allele on attention and behavior problems in adolescents exposed to alcohol during pregnancy

Neil C. Dodge [a], Joseph L. Jacobson [a,b,c], Sandra W. Jacobson [a,b,c,*]

[a] Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI, USA
[b] Department of Human Biology, University of Cape Town Faculty of Health Sciences, Cape Town, South Africa
[c] Department of Psychiatry and Mental Health, University of Cape Town Faculty of Health Sciences, Cape Town, South Africa

ARTICLE INFO

Article history:
Received 25 March 2013
Received in revised form 17 October 2013
Accepted 12 November 2013
Available online 19 November 2013

Keywords:
Fetal alcohol spectrum disorders
Prenatal alcohol exposure
Alcohol dehydrogenase
*ADH1B*3* allele
Adolescent externalizing behavior

ABSTRACT

Alcohol dehydrogenase is a critical enzyme in the metabolism of alcohol. Expression of three alleles at the *ADH1B* locus results in enzymes that differ in turnover rate and affinity for alcohol. The *ADH1B*3* allele, which appears to be unique to individuals of African descent, is associated with more rapid alcohol metabolism than the more prevalent *ADH1B*1* allele. It has been previously demonstrated that the presence of at least one maternal *ADH1B*3* allele confers a protective effect against alcohol teratogenicity in infants and children. This study was conducted to determine whether the presence of the *ADH1B*3* allele in the mother or child continues to be protective in alcohol-exposed individuals during adolescence. 186 adolescents and 167 mothers participating in a 14-year follow-up of the Detroit Longitudinal Cohort were genotyped for *ADH1B* alleles. Behavioral reports were obtained from classroom teachers. Frequencies of the *ADH1B*3* allele were 17.6% in the mothers and 21.0% in the adolescents, which are consistent with the 15–20% expected for African Americans. Prenatal alcohol exposure was associated with increased attention problems and externalizing behaviors in adolescents born to mothers with two *ADH1B*1* alleles but not in those whose mothers had at least one *ADH1B*3* allele. A similar pattern was seen in relation to the presence or absence of an *ADH1B*3* allele in the adolescent, which may have reflected the presence/absence of the maternal variant. This study is the first to demonstrate that the protective effects of the maternal *ADH1B*3* allele continue to be evident during adolescence. These persistent individual differences in vulnerability of offspring to the behavioral effects of fetal alcohol exposure are likely attributable to more rapid metabolism of alcohol that the *ADH1B*3* variant confers on the mother, leading to a reduction of the peak blood alcohol concentration to which the fetus is exposed during each drinking episode.
© 2013 Elsevier Inc. All rights reserved.

1. Introduction

Fetal alcohol spectrum disorders (FASD) include the broad range of physical and neurobehavioral outcomes associated with prenatal alcohol exposure (Hoyme et al, 2005).

Numerous alcohol-related neurocognitive deficits have been reported (e.g., Streissguth et al., 1990; Jacobson et al., 2004, 2008; J.L. Jacobson et al., 2011; S.W. Jacobson et al., 2011; Burden et al., 2005; Goldschmidt et al., 1996; Coles et al., 2010), but fewer studies have documented affective and behavioral problems. Children and adolescents prenatally exposed to alcohol exhibit parent- and teacher-reported behavioral problems (Brown et al., 1991; Carmichael Olson et al., 1997; Jacobson et al., 2006), poorer social functioning (Roebuck et al., 1999), and more internalizing and externalizing problems (Mattson and Riley, 2000; D'Onofrio et al., 2007; O'Leary et al., 2009; Disney et al., 2008), even at relatively low levels of exposure (Sood et al., 2001). Larkby et al. (2011) found that one or more drinks/day during the first trimester were associated with an increased rate of conduct disorder in adolescents.

Although FASD are associated with a broad range of adverse outcomes, not all children born to mothers who drink during pregnancy are affected. Laboratory animal studies have demonstrated that dose and timing of exposure can determine vulnerability or severity of outcome (e.g., Goodlett et al., 2005). In addition, three maternal factors have been identified as moderators of severity of fetal alcohol-related outcomes—older maternal age at delivery (May, 1991; Jacobson et al., 1996), less stimulating home environment, and maternal alcohol abuse history (Jacobson et al., 2004).

Abbreviations: AA, absolute alcohol; ADH, alcohol dehydrogenase; *ADH1B*, beta subunit of class I alcohol dehydrogenase; ADHD, attention deficit/hyperactivity disorder; ALDH, aldehyde dehydrogenase; CD, conduct disorder; DBD, disruptive behavior disorders; DSM-IV, Diagnostic and Statistical Manual—IV; MDI, Mental Development Index; ODD, oppositional defiant disorder; TRF, Teacher Report Form.

* Corresponding author at: Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, 3901 Chrysler Drive, Suite 2-C, Detroit, MI 48201, USA. Tel.: +1 313 993 5454; fax: +1 313 993 3427.
E-mail address: sandra.jacobson@wayne.edu (S.W. Jacobson).

0892-0362/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ntt.2013.11.003

The potential of genetic differences to moderate the risk of fetal alcohol related-impairment in humans has been examined for one class of polymorphisms, the *ADH1B* alleles. Alcohol is metabolized primarily in the liver by alcohol dehydrogenase (ADH), which oxidizes alcohol to acetaldehyde. Acetaldehyde is then oxidized to acetate by aldehyde dehydrogenase (ALDH) with ADH being the rate-limiting step. Functional polymorphisms in the locus encoding the beta subunit of the Class I ADH (*ADH1B*) have been found to alter rates of alcohol metabolism. The *ADH1B*1* allele, is the most prevalent form found among Caucasian and African Americans (Brennan et al., 2004). Alcohol is cleared more rapidly in individuals with either of this allele's variants—*ADH1B*2* and *ADH1B*3*—due to greater enzymatic activity of ADH, compared with individuals homozygous for the *ADH1B*1* allele (Bosron and Li, 1987). The *ADH1B*2* allele is most prevalent in Asian populations (Brennan et al., 2004) and is seen in the Cape Coloured (mixed ancestry) population of South Africa (Viljoen et al., 2001). The *ADH1B*3* allele has been identified in Americans of African descent (Osier et al., 2002) and occurs at a rate of approximately 15–20% (Bosron and Li, 1987; Brennan et al., 2004).

The three functional variants of the *ADH1B* gene have distinct pharmacokinetic properties. Both the *ADH1B*2* and *ADH1B*3* alleles have much larger maximal velocities than the *ADH1B*1* allele. *ADH1B*3* has a much larger K_m for ethanol, such that at low ethanol concentrations, it is slower than the *ADH1B*1* allele, but at high concentrations it is greater than 10-fold faster (Lee et al., 2004). Numerous studies have shown that individuals with at least one *ADH1B*2* (e.g., Carr et al., 2002) or *ADH1B*3* allele (e.g., Ehlers et al., 2007) are less likely to develop alcohol use disorders and consume less alcohol on average. Additionally, those with the *ADH1B*3* allele report higher sedation and a larger pulse-rate increase than those without the allele in response to a moderate alcohol challenge (McCarthy et al., 2010).

McCarver et al. (1997) found that fetal alcohol exposure was associated with reduced birth weight and lower Bayley Mental Development Index (MDI) scores in exposed African American infants whose mothers were homozygous for the *ADH1B*1* allele. These effects were not seen in alcohol-exposed infants of mothers with at least one *ADH1B*3*. Das et al. (2004) found protective effects of the *ADH1B*3* allele on alcohol-related facial dysmorphology when both the mother and child had a copy of the *ADH1B*3* allele (but cf. Stoler et al., 2002).

In an extensive investigation of the moderating effects of the *ADH1B*3* allele, Jacobson et al. (2006) presented data from the Detroit Longitudinal Prenatal Alcohol Exposure Cohort during infancy and at 7.5 years. Confirming McCarver et al. (1997), the effects of prenatal alcohol exposure on Bayley MDI scores were markedly less severe in children born to mothers with at least one copy of the *ADH1B*3* allele. The presence of a maternal *ADH1B*3* allele was also protective against effects on infant head circumference, symbolic development, and reaction time. At 7.5 years, protective effects were seen on measures of attention, working memory, and executive function. In children whose mothers were homozygous for the *ADH1B*1* allele, prenatal alcohol exposure was associated with increased social problems, inattention, aggressive behaviors, and hyperactivity problems on the Achenbach (1991) Teacher Report Form (TRF), effects not seen in children born to mothers with at least one *ADH1B*3* allele. By contrast, there was no systematic pattern of protective effects relating to the presence of an *ADH1B*3* allele in the child.

The purpose of this study was to extend the findings seen in the Detroit cohort in infancy and at 7.5 years by determining whether the presence of an *ADH1B*3* allele continues to have an impact on prenatal alcohol-related behavior problems in adolescence. Teacher reports were used to assess behavior problems. We hypothesized that the presence of a maternal *ADH1B*3* allele would mitigate the effects of prenatal alcohol exposure on these outcomes. At 14 years we expected to see effects on delinquency and conduct disorder not seen at 7.5 years since these behaviors become more prevalent during adolescence. Given the higher incidence of externalizing problems and attention deficit hyperactivity disorder (ADHD) in males (e.g., Biederman et al., 2002; Lahey et al., 2000), we also examined whether the effects of prenatal alcohol exposure on behavior problems in the more vulnerable adolescents lacking the *ADH1B*3* allele were stronger in males than females.

2. Methods

2.1. Participants

The sample consisted of 200 African American mother/child dyads from the Detroit Longitudinal Cohort assessed at 14 years for whom *ADH1B* allele data were available for mother and/or child. Mothers were recruited into the study between September 1986 and April 1989 during their first prenatal visit ($M = 23.4$ weeks gestation) to a large inner-city maternity hospital. Moderate- and heavy-drinking women were over-represented by including all women reporting alcohol consumption at conception averaging at least 1 standard drink/day (0.5 oz absolute alcohol (AA)/day). A random sample of approximately 5% of the lower level drinkers and abstainers was also invited to participate. To reduce the risk that alcohol might be confounded with cocaine exposure, heavy cocaine (2 days/week) light alcohol (<7 drinks/week) users were also included. Infant exclusionary criteria were birth weight <1500 g, gestational age <32 weeks, major chromosomal anomalies, neural tube defects, or multiple births.

2.2. Assessment of prenatal exposure

At each prenatal clinic visit ($M = 5.3$ visits), the mother was interviewed using a timeline follow-back protocol to determine incidence and amount of drinking on a day-by-day basis during the preceding 2 weeks (Jacobson et al., 2002). Recall was linked to specific times of day and activities. Volume was recorded for each type of alcohol beverage consumed each day, converted to oz AA, and averaged across clinic visits. Each oz of AA is equivalent to 2 standard drinks. At the first visit, the mother was also asked to recall her day-by-day drinking during a typical week around time of conception. Smoking during pregnancy was reported as average number of cigarettes/day. Detailed drug use data were also obtained at each clinic visit.

2.3. ADH genotype determination

Five drops of blood were obtained by a phlebotomist from the mother by finger-stick puncture and from the child by finger-stick or venipuncture at the 7.5- or 14-year visit and placed on diagnostic filter paper for ADH genotyping at the Indiana University School of Medicine. *ADH1B* genotypes were determined using enzymatic amplification of genomic DNA followed by hybridization with allele-specific oligonucleotides.

2.4. 14-Year assessments

Among the adolescents originally assessed in infancy, 61.3% were seen at 14 years, 89.8% of whom provided genetic samples. No differences in amount or frequency of drinking at time of conception or across pregnancy were detected between those who participated in the 14-year follow-up and those who did not (all $ps > .15$). Nor did the 14-year participants differ in socioeconomic status, maternal education, or marital status from those not followed up (all $ps > .20$); however, those who participated were born to slightly older mothers ($M = 27.0$) than those who did not ($M = 25.3$; $t(478) = 3.13$; $p < .01$). Procedures were approved by the Wayne State University Human Investigation Committee. Written informed consent was obtained from the mother at recruitment and the mother/primary caregiver at the follow-up assessments; oral assent was obtained from the children at 7.5 and 14 years. The mother and child each received a small remuneration; and the mother, child, and teacher also received a small gift. All assessments were conducted by a research assistant blind regarding

Download English Version:

https://daneshyari.com/en/article/2591047

Download Persian Version:

https://daneshyari.com/article/2591047

Daneshyari.com