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Prenatal ethanol preferentially enhances reactivity of the dopamine D_1 but not D_2 or D_3 receptors in offspring

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Abstract

Reports of prenatal ethanol (ETOH) effects on the dopamine system are inconsistent. In an attempt to clarify this issue, dams were given 35% ethanol-derived calories as the sole nutrient source in a liquid diet from the 10th through the 20th day of gestation (ETOH). Controls were pair-fed (PF) an isocaloric liquid diet or given ad libitum access to laboratory chow (LC). Prenatal exposure to both liquid diets reduced body weight of offspring relative to LC controls, more so for ETOH than for PF exposure. Prenatal ETOH also decreased litter size and viability, relative to both LC and PF control groups. On postnatal days 21–23, male and female offspring were given an injection of saline vehicle or one of eight specific dopamine receptor agonists or antagonists. Immediately after injection subjects were placed in individual observation cages, and over the following 30 min, eight behaviors (square entries, grooming, rearing, circling, sniffing, yawning, head and oral movements) were observed and quantified. No prenatal treatment effects on drug-induced behaviors were observed for dopamine D_2 (Apomorphine, DPAT or Quinpirole) or D_3 (PD 152255, Nafadotride, Apo or Quin effects on yawning) receptor agonists or antagonists, or for the vehicle control. In contrast, prenatal treatment effects were seen with drugs affecting the dopamine D_1 receptor. Both D_1 agonists (SKF 38393) and antagonists (SCH 23390 and high doses of spiperone) altered behaviors, especially oral and sniffing behaviors, in a manner which suggested enhanced dopamine D_1 drug sensitivity in both ETOH and PF offspring relative to LC controls. These results suggest that at this age, both sexes experience a prenatal undernutrition-linked increase in the behavioral response to dopamine D_1 agonists and antagonists, which can be intensified by gestational exposure to alcohol.

Keywords: Prenatal ethanol exposure; Dopamine receptor subtypes; Drug challenge; Dopamine agonists; Dopamine antagonists; Sex factors; Fetal growth retardation; Undernutrition

1. Introduction

Maternal consumption of alcohol during pregnancy can have profound teratological effects on the developing fetus. The spectrum of enduring manifestations are extensive and lie along a continuum, from fetal alcohol syndrome (FAS), which is defined by pre- and/or postnatal growth retardation, characteristic facial dysmorphology, and abnormal function of the central nervous system (CNS), to other alcohol-related birth deficits (ARBD), which range from severe behavioral and cognitive dysfunction to minimal deficit [1,2,44].

The most devastating and far-reaching consequences of prenatal exposure to alcohol is its effect on the brain and the ensuing behavioral alterations that occur [60,90]. CNS dysfunction, one of the more consistent and persistent outcomes, is expressed as mental retardation, developmental delay, attention deficits, hyperactive behavior, impulsivity, hyper-responsiveness to stress, poor motor coordination, and learning disabilities [53]. While neuropathology is most

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often the result of heavy prenatal alcohol exposure, altered CNS function can occur even after relatively modest amount of alcohol exposure and can persist into adolescence and adulthood [79].

Although there is a considerable amount of data regarding the morphological and behavioral effects associated with prenatal alcohol exposure, the mechanisms underlying developmental defects caused by maternal ETOH consumption remain unclear [55]. Animal models, which mirror many of the physical anomalies and behavioral abnormalities observed clinically, have been used to define the neurochemical abnormalities that result from in utero ethanol exposure. These investigations have found ethanol-induced impairments in the development of most CNS neurotransmitter systems, including serotonin, norepinephrine, glutamate, γ-aminobutyric acid, acetylcholine, histamine and opiate peptides [5,6,41,53,60,78,90,91,108]. However, neurochemical, behavioral and pharmacological studies suggest that developing dopaminergic systems may be particularly targeted [41,95]. Prenatal ethanol exposure impairs the synthesis and/or secretion of dopaminergic trophic factors, which are essential for normal CNS development [75,111], and the ability of such factors to mediate differentiation and neurite elongation, thus adversely affecting subsequent neural development in dopaminergic and other systems [39]. Animal studies reveal that both chronic and episodic in utero exposure to ETOH results in structural abnormalities in the caudate nucleus and the cerebellum [7,42]. At the cellular level, Shetty et al. [106] found dendritic dysmorphology in the substantia nigra pars compacta of prenatally ETOH exposed rats.

A very wide range of effects/no effects are reported for whole brain and/or regional content of DA and its metabolites. Gestational exposure to ethanol decreases basal concentrations of DA and its metabolite DOPAC in brain regions that are targets of dopaminergic projections, as well as those that contain cell bodies of dopaminergic neurons, increases tyrosine hydroxylase activity, alters DA receptor binding, adversely impacts the development of dopamine reuptake sites, and reduces the spontaneous activity of ventral tegmental area dopamine neurons [19,29,34,35,38,49,53,63,74,89,95,108,113,127]. Therefore, the reduction of DA in target areas combined with a decreased concentration of reuptake sites suggests that exposure of the fetus to ethanol impairs the development of DA projections [37]. Morphological changes in DA neurons, including smaller cell bodies and retarded dendritic growth and branching, [106], as well as decreased activity in substantial nigra/VTA neurons [105,127] provide support for this hypothesis.

However, despite the evidence suggesting that prenatal ethanol produces a hypofunctioning in DA systems, there is also a body of literature indicating no changes in DA, DOPAC or HVA in the whole brain or striatum and nucleus accumbens [18,19,27,28,78,83,96,115] or striatal DA reuptake sites [53]. Moreover, there is some indication that prenatal ETOH exposure increases activity in central DA systems [20,49,76]. These inconsistencies emphasize the need for further research in this area.

The selectivity of prenatal alcohol on dopamine systems is further suggested by the impact of this treatment on the number of functional dopamine receptors subtypes in the rodent brain. However, changes are age, sex, receptor subtype and species specific. Prenatal ETOH both decreases [38] and increases [53] D_1 binding sites in the striatum and / or frontal cortex. In mouse, striatal D_1 receptors are increased [19]. In both mice and rats, the effects on the D_1 receptor subtype occur early in development and are transient [19,38]. Both no change [19,38] or a significant reduction in D_2 binding sites have been reported in the striatum following prenatal ETOH [76,77,89,95]. These divergent findings prohibit the formulation of a definitive hypothesis regarding ethanol's effect on DA receptor subtypes.

Behavioral and pharmacological studies also indicate that prenatal ethanol exposure affects dopaminergic systems in the CNS. Rats and mice prenatally exposed to alcohol show alterations in behaviors supported by normal dopaminergic function, such as motor activity, catalepsy and stereotypy, motor coordination and reward-seeking behaviors (see Ref. [19] for review). Moreover, studies with acute and chronic drug challenges suggest that prenatal alcohol profoundly alters the behavioral response to dopaminergic drugs. Altered sensitivity of the DA receptor is supported by reports that rats exposed to ethanol prenatally show enhanced responsiveness to the indirect acting CNS stimulants, amphetamine and methylphenidate, with increased peak exploratory behavior, stereotypies and unilateral rotational behavior [17,48,81,119]. In contrast, sensitization of locomotor activity to repeated intermittent methylphenidate in adult rat offspring is unchanged [95], and amphetamine challenge reduced peak activity [76]. In addition to motor activity, lever pressing for a food reward is more disrupted by amphetamine in adult and middle-aged prenatal ethanol exposed male mice than controls [51,52].

Similarly, prenatal ethanol exposure affects the response to dopamine receptor agonists and antagonists. The D_1/D_2 mixed agonist, apomorphine, increased stereotypy in adult male rat prenatally exposed to ETOH [48]. It also induced greater locomotor activity at low doses but lower activity at high doses in prenatal ETOH exposed males, while female offspring showed less of an increase in this behavior than controls following high doses of the drug [62]. Although the direction of the response to apomorphine is opposite, the does–response effect seen in ethanol-exposed mice is similar to that seen in rat offspring. At higher doses, mice are less sensitive to the locomotor suppressant effect of apomorphine on baseline and ethanol-stimulated locomotor activity, but exhibited greater sensitivity to the suppressant effects of low doses of the drug [12]. Moreover, the D_2 antagonist, haloperidol, produced a greater decrease in