Alcohol 51 (2016) 1–15

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

The impact of prenatal alcohol exposure on social, cognitive and affective behavioral domains: Insights from rodent models

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ARTICLE INFO

Article history:
Received 11 September 2015
Received in revised form
11 December 2015
Accepted 11 December 2015

Keywords:
Executive function
Social behavior
Spatial and temporal memory
Anxiety and motor learning
Preclinical models

ABSTRACT

Fetal Alcohol Spectrum Disorders (FASD) are characterized by deficits in working memory, response inhibition, and behavioral flexibility. However, the combination and severity of impairments are highly dependent upon maternal ethanol consumption patterns, which creates a complex variety of manifestations. Rodent models have been essential in identifying behavioral endpoints of prenatal alcohol exposure (PAE). However, experimental model outcomes are extremely diverse based on level, pattern, timing, and method of ethanol exposure, as well as the behavioral domain assayed and paradigm used. Therefore, comparisons across studies are difficult and there is currently no clear comprehensive behavioral phenotype of PAE. This lack of defined cognitive and behavioral phenotype is a contributing factor to the difficulty in identifying FASD individuals. The current review aims to critically examine preclinical behavioral outcomes in the social, cognitive, and affective domains in terms of the PAE paradigm, with a special emphasis on dose, timing, and delivery, to establish a working model of behavioral impairment. In addition, this review identifies gaps in our current knowledge and proposes future areas of research that will advance knowledge in the field of PAE outcomes. Understanding the complex behavioral phenotype, which results from diverse ethanol consumption will allow for development of better diagnostic tools and more critical evaluation of potential treatments for FASD.

Introduction

Beginning with the first reports that prenatal alcohol exposure (PAE) could have severe and long-lasting consequences on the neurobehavior of offspring (Jones, 1975; Jones & Smith, 1973), there has been a consistent focus on identifying how alcohol affects the developing fetus and delineating the spectrum of behavioral changes. Although there is an increasing awareness that high levels of alcohol consumption during pregnancy can impair growth, cognition, and social behavior of the child, PAE remains one of the most common developmental insults (Day et al., 2002; Green et al., 2009; Thomas, Kelly, Mattson, & Riley, 1998). Recent reports suggest that as many as one–third of women drink at some time during pregnancy, and between 5 and 10% report binge drinking incidents (Ethen et al., 2009). There is a growing consensus that even moderate alcohol intake during pregnancy, which is the more common pattern, can lead to lasting cognitive impairments even when growth and morphological changes are absent. These impairments, which fall under the category of Fetal Alcohol Spectrum Disorder (FASD), may not be evident until early adolescence and are characterized by impairments in working memory, response inhibition, and behavioral flexibility (Green et al., 2009; Mattson, Goodman, Caine, Delis, & Riley, 1999; Streissguth et al., 1991). Rodent models have become an important tool for studying the effects of alcohol on development at all levels, particularly as studies in human patients and rodent models suggest a congruent effect of blood alcohol concentration (BAC) on behavioral outcomes across species (Driscoll, Streissguth, & Riley, 1990).

Rodent models are an indispensable tool for studying causal factors of prenatal exposure effects, for several reasons: 1) inbred strains of mice and rats are genetically homogenous populations, with which the issue of genetic heterogeneity in epidemiological studies can be largely circumvented, making it more feasible to parcel out impacts of environmental factors; 2) environmental insults, such as alcohol, can be strictly timed and given in exact quantities, enabling the discoveries of sensitive time windows and threshold of harmful doses; 3) the impacts of environmental factors

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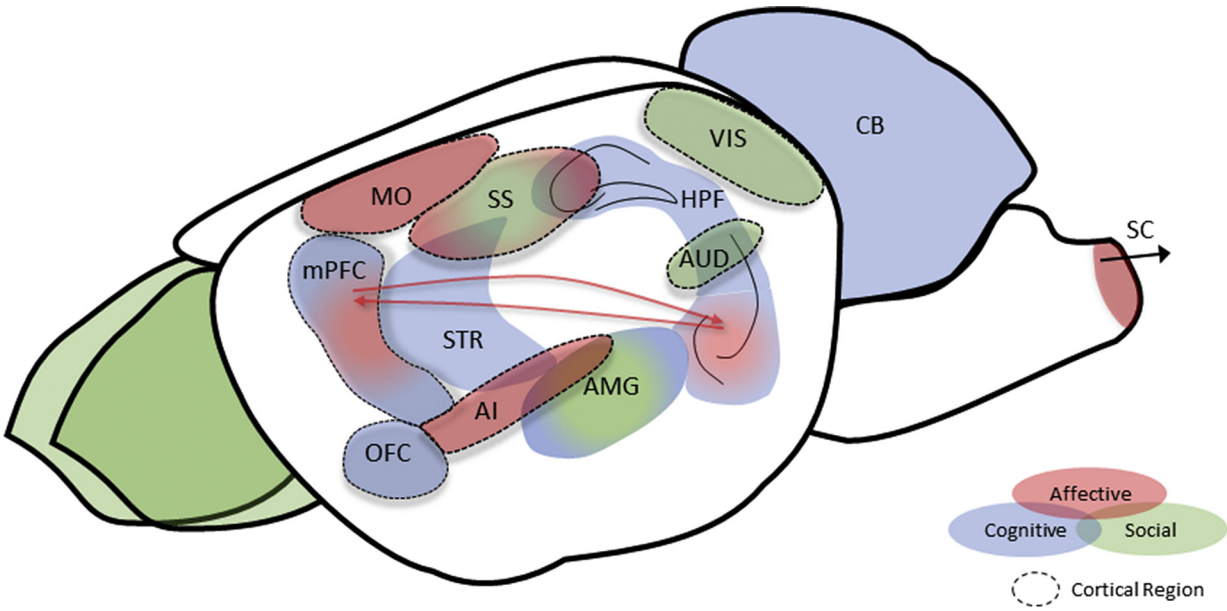
http://dx.doi.org/10.1016/j.alcohol.2015.12.002
0741-8329/

can be tested on the behavioral level, as well as on neuroanatomical, neurochemical, and neuronal levels, enabling the discovery of the effects of certain environmental insults on the whole organism; and 4) cross-species comparisons ensure that results are applicable and generalizable in different species. These studies have identified several factors that are involved in the impact of PAE including *method of delivery*, *level of exposure*, *pattern of exposure*, and *timing of exposure* during development.

Here we review the available literature on the behavioral impacts of PAE in rodent models, from early studies to the most recently published, with the goal of providing a comprehensive behavioral phenotype spanning the *social, affective, and cognitive* domains (Fig. 1). Although alcohol was recognized as a teratogen in 1973, it was not until 2002 that the CDC began developing diagnostic guidelines for FAS and FASD (Williams, Smith & Committee on Substance Abuse, 2015). However, in 2015, in a cohort of foster children who were referenced to a mental health clinic for behavioral disorders, 86.7% were either previously undiagnosed or misdiagnosed (Chasnoff, Wells, & King, 2015). FASD is commonly misdiagnosed with other conditions such as attention deficit hyperactivity disorder (ADHD) or Autism Spectrum Disorder, because behavioral profiles can be similar (Bishop, Gahagan, & Lord, 2007; Peadon & Elliott, 2010). However, it should be noted that ADHD has been estimated to be co-morbid with FASD in up to 94% of individuals (Peadon & Elliott, 2010). Being able to fully characterize the FASD behavioral and cognitive phenotype based on approximate exposure level and timing would greatly improve diagnosis and therefore treatment, particularly early intervention. Therefore, this review seeks to highlight areas in which more concentrated research using rodent models is needed to fill in the missing framework.

Timing, dose, and delivery

Rodent studies have aimed to replicate prenatal exposures in humans using a variety of delivery methods including intraperitoneal (i.p.) injection, oral gavage, intragastric gavage, liquid diets, voluntary drinking, limited-access models, and vaporized alcohol inhalation (for a comprehensive review see Patten, Fontaine, & Christie, 2014). These techniques have been used to produce a wide range of doses as measured by Blood Alcohol Concentration (BAC). The question of what is considered heavy versus moderate exposure in humans and rodents is still not widely agreed upon, due to differences in alcohol metabolism, and the effects that



EXPOSURE	SOCIAL		AFFECTIVE		COGNITIVE		
	MATERNAL	CONSPECIFIC	ANXIETY	LOCOMOTION	SPATIAL	REVERSAL	PAVLOVIAN
1st -3rd Trimester							
Moderate	Not Impaired	Impaired	Increased	Decreased	Impaired	NT	NT
Heavy	Impaired	Impaired	NT	NT	Impaired	NT	NT
1st +2nd Trimester							
Moderate	Impaired	Impaired	None → Increased	Impaired	Only on complex	Impaired	Impaired
Heavy	NT	Impaired	NT	Impaired	Impaired	NT	NT
3rd Trimester Only							
Moderate	NT	NT	NT	NT	Mod. Imp (age effects)	Impaired	NT
Heavy	NT	NT	Decreased	Increased	Impaired	NT	Impaired

Fig. 1. Regions of interest for behavioral domains and summary of behavioral effects in rodent models of PAE. Primary areas of the rodent brain that have been implicated in social, affective, and cognitive behaviors across species are reviewed in Figs. 2–7. These regions may make unique targets for PAE, especially regions implicated in more than one class of behaviors (indicated by double-color shading). The tables summarize the overall conclusion of the effect of PAE on behavioral domains reviewed, based on the three most prominent exposure timelines utilized. NT = not tested, MO = primary motor area, SS = somatosensory area, VIS = primary visual cortex, AUD = auditory cortex, AI = agranular insular cortex, OFC = orbital frontal cortex, mPFC = medial prefrontal cortex, SC = spinal cord, CB = cerebellum, HPF = hippocampal formation, STR = striatum, AMG = amygdala.