BIOGRAPHICAL SKETCH

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NAME: Parnell, Scott E.

eRA COMMONS USER NAME (agency login): scott_parnell

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Texas A&M University, College Station, TX	BA	08/1998	Biology
Texas A&M University, College Station, TX	PHD	11/2004	Medical Sciences/Neuroscience
University of North Carolina, Chapel Hill, NC	Postdoctoral Fellow	09/2009	Neurotoxicology/Embryology

A. Personal Statement

Research in my laboratory is focused on understanding the pathology and related pathogenic mechanisms underlying prenatal alcohol exposure (PAE) and other teratogens during early gestation. PAE induces a wide spectrum of deficits depending on a multitude on factors, including timing and amount of exposure, genetics, etc. In order to better understand this spectrum of effects, part of my research has been aimed at understanding the developmental stage-dependent effects of early PAE on the structure and function of the central nervous system. Using a mouse model of FASD, high-resolution magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) and a behavioral phenotyping battery, my lab works to define the developmental stage-dependent effects of ethanol exposure during early gestation with the goal of improving clinical diagnosis, as well as uncovering pathogenic mechanisms. Towards this latter goal, a large part of my lab's focus is on the cellular events following ethanol exposure that lead to the observed dysmorphologies. Alongside this research using genetically engineered mice and whole transcriptome sequencing (RNA-seq), we also aim to better understand the genes that alter susceptibility to the detrimental effects of early PAE.

B. Positions and Honors

Positions and Employment

1998 - 1999 Research Assistant, Dept. of Human Anatomy and Medical Neurobiology, Texas A&M University, College Station, TX

1999 - 2004 Graduate Research Assistant, Dept. of Human Anatomy and Medical Neurobiology, Texas A&M University, College Station, TX

2004 - 2004 NIH Predodoctoral Fellow, NIAAA

2004 - 2009 Postdoctoral Research Fellow, Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC

2009 - 2012 Research Assistant Professor, Dept. of Cell and Developmental Biology, Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC

2012 - Assistant Professor, University of North Carolina, Dept. of Cell Biology and Physiology, Bowles Center for Alcohol Studies, Carolina Institute for Developmental Disabilities, University of North Carolina, Chapel Hill, NC

Other Experience and Professional Memberships

1998 - Member, Research Society on Alcoholism

2011 - Member, American Association of Anatomists
2014 - Member, Teratology Society
2015 - Member, RSA Education Committee

Honors

2008 Junior Investigator Award, International Conference on Applications of Neuroimaging to Alcoholism (ICANA)

C. Contribution to Science

1. Nicotine lowers blood alcohol concentrations (BAC).

   Ethanol (alcohol) and nicotine are the two most commonly co-abused drugs, so it is natural to study their teratogenicity together. In one of these initial studies in a rat model of third trimester ethanol exposure, we discovered that when ethanol and nicotine were administered together, the peak BAC was lower in these pups compared to pups administered ethanol alone (Chen et al., 1998). In a follow-up study in neonatal rat pups, we confirmed this finding that nicotine lowers BACs and demonstrated that it does so in a dose-dependent manner (Chen et al., 2001). Although these findings were exciting, it was unknown if this phenomenon was isolated to neonatal ages and the mechanism by which nicotine lowered BACs was unclear. To answer these questions, we then co-administered nicotine and ethanol in adult rats who demonstrated a similar response to the neonates (Parnell et al., 2006). It was previously known that nicotine was able to slow gastric emptying, so we hypothesized that nicotine lowered BACs by prolonging the time that ethanol remained in the stomach undergoing metabolism via gastric alcohol dehydrogenase (gADH) prior to being absorbed via the small intestine. To test this hypothesis, we conducted an experiment in which we demonstrated that nicotine could only lower peak BACs when ethanol was administered intragastrically as opposed to it being given through an intraperitoneal injection, thus bypassing the stomach. These novel findings were the first to show that nicotine could lower BACs.

   a. Chen WJ, Parnell SE, West JR. Neonatal alcohol and nicotine exposure limits brain growth and depletes cerebellar Purkinje cells. Alcohol. 1998 Jan;15(1):33-41. PubMed PMID: 9426835.
   b. Chen WJ, Parnell SE, West JR. Nicotine decreases blood alcohol concentration in neonatal rats. Alcohol Clin Exp Res. 2001 Jul;25(7):1072-7. PubMed PMID: 11505035.
   c. Parnell SE, West JR, Chen WJ. Nicotine decreases blood alcohol concentrations in adult rats: a phenomenon potentially related to gastric function. Alcohol Clin Exp Res. 2006 Aug;30(8):1408-13. PubMed PMID: 16899044.

2. Lack of hypoxia in late gestation.

   Based on a few early studies in various animal models of FASD, it was concluded that third trimester ethanol exposure induced brain damage through an ethanol-induced induction of hypoxia. Since then, many studies have examined ways in which PAE may induce hypoxia with the hope to find a way to prevent this phenomenon. Through a series of carefully controlled experiments in a novel sheep model of FASD, we demonstrated that ethanol exposure induces significant brain damage in the absence of reductions in oxygen levels or blood flow. These studies have been in significant in that they have largely ruled out an over studied mechanism of ethanol's late gestation pathogenesis.

   a. Cudd TA, Chen WJ, Parnell SE, West JR. Third trimester binge ethanol exposure results in fetal hypercapnea and acidemia but not hypoxemia in pregnant sheep. Alcohol Clin Exp Res. 2001 Feb;25(2):269-76. PubMed PMID: 11236842.
   b. West JR, Parnell SE, Chen WJ, Cudd TA. Alcohol-mediated Purkinje cell loss in the absence of hypoxemia during the third trimester in an ovine model system. Alcohol Clin Exp Res. 2001 Jul;25(7):1051-7. PubMed PMID: 11505032.
   c. Parnell SE, Ramadoss J, Delp MD, Ramsey MW, Chen WJ, West JR, Cudd TA. Chronic ethanol increases fetal cerebral blood flow specific to the ethanol-sensitive cerebellum under normoxaemic,

hypercapnic and acidaemic conditions: ovine model. Exp Physiol. 2007 Sep;92(5):933-43. PubMed PMID: 17526556.

3. Prevention of ethanol-induced brain defects.

   Prenatal alcohol exposure is one of the leading causes of birth defects, and research is continually finding new ways in which alcohol can harm the developing brain. In spite of these facts and ongoing, robust prevention campaigns, the incidence of FASD has not changed. In order to test potential therapeutic strategies, we tested the ability of two compounds to ameliorate the effects of early PAE. For this series of experiments, we used a FASD mouse model that we developed involving dietary ethanol exposure that demonstrated consistent ethanol-induced ocular defects as a measure of ethanol's teratogenesis as eye and forebrain development is intimately linked in early development. (Parnell et al., 2006). First we tested the efficacy of SAL (SALLRSIPA), a nine amino acid fragment of activity-dependent neurotrophic factor (ADNF). When administered in the ethanol-containing liquid diet during early gestation (gastrulation and neurulation), SAL reduced the incidence of eye defects to a level approximately two-thirds that of ethanol alone; a level not much higher than the spontaneous incidence of eye defects in this mouse strain (Parnell et al., 2007). The second compound we tested was n-acetylcysteine (NAC), a drug used to increase glutathione level. Using the same mouse model and exposure paradigm in the previous SAL study, we demonstrated that NAC could also ameliorate the effects, although to a lesser extent compared to SAL (Parnell et al., 2010). However, these data do begin to suggest cellular mechanisms such as altered reactive oxygen species (ROS) homeostasis that may underlie ethanol's pathogenesis.

   a. Parnell SE, Dehart DB, Wills TA, Chen SY, Hodge CW, Besheer J, Waage-Baudet HG, Charness ME, Sulik KK. Maternal oral intake mouse model for fetal alcohol spectrum disorders: ocular defects as a measure of effect. Alcohol Clin Exp Res. 2006 Oct;30(10):1791-8. PubMed PMID: 17010146.
   b. Parnell SE, Chen SY, Charness ME, Hodge CW, Dehart DB, Sulik KK. Concurrent dietary administration of D-SAL and ethanol diminishes ethanol's teratogenesis. Alcohol Clin Exp Res. 2007 Dec;31(12):2059-64. PubMed PMID: 17949468.
   c. Parnell SE, Sulik KK, Dehart DB, Chen SY. Reduction of ethanol-induced ocular abnormalities in mice through dietary administration of N-acetylcysteine. Alcohol. 2010 Nov-Dec;44(7-8):699-705. PubMed PMID: 21112471; PubMed Central PMCID: PMC2993176.

4. Adaptation of high-resolution MRI to an FASD animal model of stage-dependent defects.

   PAE induces a wide spectrum of deficits depending on several factors that have been shown to modify ethanol's teratogenesis, the most important of which is probably timing of exposure, particularly during early gestation (gastrulation – neurulation stages) when the brain is undergoing key formative processes. This is reflected in the fact that gastrulation stage PAE (gestational day [GD] 7 in the mouse) results in the classic craniofacial features associated with FAS and brain defects in the holoprosencephaly (HPE) spectrum, however, exposure just one day later (GD 8) at the start of neurulation induces more subtle defects. In order to better understand the stage-specific effects of early gestational PAE, we began a series of experiments in which we exposed pregnant mice at varying stages of their pregnancy and then examined the offspring to determine the resultant brain malformations. For this, we pioneered the use of high-resolution magnetic resonance imaging (MRI – sometimes referred to as magnetic resonance microscopy) which uses high field strength magnets (7-9.4 T) to obtain images at resolutions of 10-50 □m. This allows for a detailed examination of the specific pattern of regional brain changes resulting from varying patterns of acute ethanol exposure. In contrast to the HPE brain and facial phenotypes observed following a GD 7 (gastrulation) exposure that resulted from a general lack of midline tissue, PAE during neurulation resulted in only eye defects in the face, along with more subtle, yet consistent defects in the brain (Parnell et al., 2009, 2013; O'Leary-Moore et al., 2010). The more significant effects include dysgenesis of the cerebellum and a consistent rostroventral midline expansion, an opposite effect relative to exposure during gastrulation. Although there were small variations in regional brain effects across the days of exposure during neurulation (GD 8, 9, 10), the effects on the rostroventral midline expansion were consistent in all of these exposure periods, suggesting a neurulation-stage specific dysmorphology. Furthermore, this midline expansion has also been replicated in our diet exposure model in which a moderate level of ethanol exposure throughout the period of neurulation resulted in similar effects. This is

significant as it demonstrated a pathogenic origin of PAE-induced hypertelorism observed in some children with FASD and provides clues to a basic cellular mechanism underlying this pathology.

a. Parnell SE, O'Leary-Moore SK, Godin EA, Dehart DB, Johnson BW, Allan Johnson G, Styner MA, Sulik KK. Magnetic resonance microscopy defines ethanol-induced brain abnormalities in prenatal mice: effects of acute insult on gestational day 8. Alcohol Clin Exp Res. 2009 Jun;33(6):1001-11. PubMed PMID: 19302087; PubMed Central PMCID: PMC2748865.

b. O'Leary-Moore SK, Parnell SE, Godin EA, Dehart DB, Ament JJ, Khan AA, Johnson GA, Styner MA, Sulik KK. Magnetic resonance microscopy-based analyses of the brains of normal and ethanol-exposed fetal mice. Birth Defects Res A Clin Mol Teratol. 2010 Nov;88(11):953-64. PubMed PMID: 20842647; PubMed Central PMCID: PMC3445267.

c. Parnell SE, Holloway HT, O'Leary-Moore SK, Dehart DB, Paniaqua B, Oguz I, Budin F, Styner MA, Johnson GA, Sulik KK. Magnetic resonance microscopy-based analyses of the neuroanatomical effects of gestational day 9 ethanol exposure in mice. Neurotoxicol Teratol. 2013 Sep-Oct;39:77-83. PubMed PMID: 23911654; PubMed Central PMCID: PMC3795920.

d. Parnell SE, Holloway HE, Baker LK, Styner MA, Sulik KK. Dysmorphogenic effects of first trimester-equivalent ethanol exposure in mice: a magnetic resonance microscopy-based study. Alcohol Clin Exp Res. 2014 Jul;38(7):2008-14. PubMed PMID: 24931007; PubMed Central PMCID: PMC4107075.

5. Teratogenicity of synthetic cannabinoids

Marijuana and natural cannabinoids have long been suspected of altering brain development, but the results have been either subtle or mixed, depending on the variable being examined. However, through selective breeding, THC concentrations in marijuana is increasing leading to increased potencies and toxicity in adults. Perhaps more alarming, over the course of the last several years, synthetic cannabinoids are increasingly being abused. These synthetic cannabinoids have efficacies for the cannabinoid receptors as much as 50 times that of THC, leading to a greater degree of toxicity and emergency room visits by people abusing these drugs. To see if this same toxicity might extend to the developing embryo, we tested the teratogenicity of a prototypical synthetic cannabinoid, CP-55,940, in a mouse model at the beginning of neurulation, a very sensitive period in development. In this study, we discovered that synthetic cannabinoids are extremely teratogenic, inducing birth defects of the brain and craniofacies (eyes, lips, palate, etc) at dosages as low as 0.0625 mg/kg, a dose well within the range of human exposure. Together, these data clearly indicate a need for further developmental evaluation of these synthetic cannabinoids and an increased awareness of their potential impact on public health.

a. Gilbert MT, Sulik KK, Fish EW, Baker LK, Dehart DB, Parnell SE. Dose-dependent teratogenicity of the synthetic cannabinoid CP-55,940 in mice. Neurotoxicol Teratol. 2015 Dec 18;PubMed PMID: 26708672.

Complete List of Published Work in My Bibliography:
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D. Research Support

Ongoing Research Support

R00 AA018697-05
Parnell, Scott (PI)
02/01/10-08/31/16
Neuroanatomical/Functional Correlates in an FASD Model
Role: PI