

Vulnerability of the Developing Brain to Endocrine-Active Compounds

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The long-term goal of this project is to investigate the impact of early exposure to endocrine-active compounds (EACs) on brain development. Perinatal estradiol acts on the developing mammalian brain to sexually differentiate forebrain circuits, allowing for the expression of sex-specific neuroendocrine and behavioral profiles during adulthood. A growing body of evidence suggests that the developing brain may also be sensitive to the influences of EACs in the environment. Because compounds with known estrogenic or antiandrogenic properties exert adverse effects on reproduction when administered perinatally at high doses, the possibility that EACs may perturb sex-specific developmental processes in the brain is one of increasing concern. However, the extent to which these compounds are capable of influencing estrogen responsive brain areas during development, and the potential for them to permanently disrupt sexually dimorphic brain circuits, remains largely unexplored. To begin to address these questions, we are investigating the effects of estrogenic EACs on the development of a limbic-hypothalamic circuit that regulates gonadotropin release in adults. To test the hypothesis that early exposure to low doses of estrogenic compounds may influence brain development, we administered wide dose ranges of estrogen and two estrogenic EACs, genistein and bisphenol-A, to neonatal male and female rats. Our research addresses four experimental goals: (1) to determine the extent to which estrogen receptors in the neonatal rat brain are bound by each compound; (2) to determine the degree to which estrogenic EACs initiate estrogen-mediated gene expression events during development; (3) to investigate whether EAC exposure during development can alter the neuroanatomy of reproductively relevant forebrain circuits; and (4) to correlate perinatal exposure to physiologically relevant EAC doses with measures of neuroendocrine function in the adult.

Implications: In mammals, the developing brain is shaped by androgens and estrogens and may be vulnerable to certain EACs in the environment. This project studied the development of brain circuits that vary between male and female rats and that are known to regulate reproductive behavior and function. The goal researched biochemical, anatomical, and physiological measures to assess more accurately the impact of environmentally relevant EAC exposures on normal brain development and improve risk assessment methods for these endpoints.

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Presentations:

Polston, E. K. (2004). Endocrine-active compounds (EACs) and development of sexually dimorphic forebrain circuits. Poster presentation at the Annual Science Meeting of the Long-Range Research Initiative, American Chemistry Council, Miami, FL, May 5–6, 2004.

Polston, E. K. and Simerly, R. B. (2004). Ontogeny of projections from the AVPV to GnRH neurons and GnRH neuronal activation. Poster presentation at the 34th Annual Society for Neuroscience meeting, San Diego, CA, October 26, 2004.

Fortino, A. E. and Polston, E. K. (2005). Characterization of a novel neuronal population associated with gonadotropin-releasing hormone neurons. Poster presentation at the Annual Meeting of the Society for Neuroscience, Washington, DC, November 12–16, 2005.

Fortino, A. E. and Polston, E. K. (2005). Functional development of gonadotropin-releasing hormone

neurons in the female rat. Poster presentation at the Annual Meeting of the Society for Behavioral Neuroendocrinology, Austin, TX, June 22–25, 2005.

Patisaul, H. B., Fortino, A. E., and Polston, E. K. (2005). Sexual differentiation of the rodent AVPV is disrupted by neonatal exposure to genistein or bisphenol A. Poster presentation at the Annual Meeting of the Society for Behavioral Neuroendocrinology, Austin, TX, June 22–25, 2005.

Polston, E. K., Fortino, A. E., and Patisaul, H. B. (2005). Sex and the brain: Evaluating sex differences in neuroendocrine and behavior circuits. Platform presentation at the 22nd International Toxicology Conference, Research Triangle Park, NC, September 11–14, 2005.

Patisaul, H. B., Fortino, A. E., and Polston, E. K. (2006). Neonatal exposure to genistein or bisphenol-A disrupts estrous cyclicity and sexual differentiation of the brain in rodents. Poster presentation at the 15th Annual Meeting of the Triangle Consortium for Reproductive Biology, Chapel Hill, NC, February 11; 2006.

Patisaul, H. B., Fortino, A. E., and Polston, E. K. (2006). Neonatal exposure to genistein or bisphenol-A disrupts estrous cyclicity and sexual differentiation of the brain in rodents. Poster presentation at the Women's Health Research Day, University of North Carolina at Chapel Hill, Chapel Hill, NC, April 4, 2006.

Peer-reviewed publications:

Patisaul, H. B. (2005). Phytoestrogen action in the adult and developing brain. *Journal of Neuroendocrinology* 17(1): 57–64.

Patisaul, H. B., Fortino, A. E., and Polston, E. K. (2006). Neonatal genistein or bisphenol-A exposure alters sexual differentiation of the AVPV. *Neurotoxicology and Teratology* 28: 111–118.

Polston, E. K. and Simerly, R. B. (2006). Ontogeny of the projections from the anteroventral periventricular nucleus of the hypothalamus in the female rat. *Journal of Comparative Neurology* 495: 122–132.

Patisaul, H. B., Fortino, A. E., and Polston, E. K. (2007). Differential disruption of nuclear volume and neuronal phenotype in the preoptic area by neonatal exposure to genistein and bisphenol-A. *Neurotoxicology* 28: 1–12.

Polston, E. K. and Fortino, A. E. Functional development of the gonadotropin-releasing hormone neuronal system in the female rat. *Endocrinology*. (Submitted).

Other publication(s): None to date.

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