

FASD, Stress and Mental Health

Courtney R. Green, PhD and Amy Salmon, PhD

Canada Fetal Alcohol Spectrum Disorder Research Network

Issue

Fetal Alcohol Spectrum Disorder (FASD) is a neurodevelopmental disorder resulting from prenatal alcohol exposure (PAE). Individuals with FASD can experience complex behavioural and intellectual problems that persist throughout the lifespan, and can become increasingly complicated, even when supported. Over the last few decades, further research has begun to reveal a close relationship among PAE, stress pathways and mental health.

Background

Stress is a biological and psychological phenomenon that occurs in response to situations where we feel unable or unprepared to cope. It serves an important function in normal life, as it activates our "fight or flight" response, which is characterized by increased heart rate, increased breathing, increased glucose release (e.g., energy) and decreased digestion. While these responses enabled our ancestors to flee life-threatening situations, today they underpin activities such as completing tasks (e.g., meeting deadlines, giving presentations, writing exams), handling major life events (e.g., divorce, moving homes, new babies) and providing increased resources for physical activities (e.g., labour, sports).

Not surprisingly, there are complex pathways in the brain that mediate the recognition of stress and the responses [1, 2]. If the situation is considered stressful, then a specific part of the brain called the **hypothalamus** (at the base of the brain) becomes activated. The hypothalamus controls the stress response and when activated, sends signals to two other parts of the body: the pituitary gland and the adrenal medulla (located on top of the kidneys). This pathway is called the **Hypothalamic Pituitary-Adrenal (HPA)** system. The final product of the HPA system is the major stress hormone: cortisol. **Cortisol** enables the body to maintain a steady supply of blood sugar that can help cope with stress and helps the body return to a normal steady state. Cortisol also suppresses the immune system and high levels can impact memory. Recently, the association between HPA dysfunction and mental health disorders has been proposed.

Prenatal Stress

Over the last decade, research studies have provided evidence suggesting that stressful experiences during pregnancy exert long-term consequences on the future mental wellbeing of both the mother and her baby [3]. Both human epidemiological and animal studies indicate that stressful experiences in utero or during early life can increase the risk of neurological and psychiatric disorders. Stress, malnutrition and physical inactivity are three behaviours that can also influence immune and central nervous system function in both the mother and fetus, and may influence their respective risks for neurodevelopmental or psychiatric disorders [4]. Trauma experiences in the early years of life have been shown to impact early cognitive development, and this effect persists into later childhood [5]. For individuals with FASD, PAE may have an additive effect to prenatal and early postnatal stress rendering them at increased risk for developing physical and mental health problems.

Animal Studies

The effects of PAE on the HPA system have been extensively studied in animal models, including models of FASD, an now provide support for the role of abnormal cortisol levels as a predictor of mental health disorders, such as depression and anxiety [6]. These studies show that animals, who are prenatally exposed to alcohol, demonstrate persistent attention difficulties as well as unique behavioural profiles. These in turn suggest there are specific time points during development when cells are particularly vulnerable to injury of the HPA systems from PAE [7]. Specially, PAE leads to abnormal regulation of the HPA system and its interaction with dopamine – a brain chemical that helps control the reward and pleasure centres, as well as emotional response – leading to changes in how animals respond to stress. This may provide further insight into the possible mechanism underlying mental health problems associated with FASD [8-10]. Furthermore, the effects of PAE on the HPA system (i.e., changes to stress responsivity) may underlie the susceptibility of those with FASD to depression and anxiety disorders in adulthood [11]. Interestingly, a recent review comparing outcomes for male and female rats revealed that the effects of PAE and stress produce different responses and may help explain specific gender differences observed in humans [12]. These changes in the HPA system caused by PAE may be the reason for the hyper-responsivity to stress and increased mental health conditions commonly experienced by individuals with FASD.

Human Studies

The number of maternal drinking days from conception to pregnancy recognition has been correlated with increased cortisol reactivity, elevated heart rate and negative affect in infants, all of which are signs of greater activation of the stress response system [13]. However, some studies have also shown a blunted response to an acute stress event in alcohol-exposed newborns [14]. PAE has been reportedly related to elevated levels of cortisol in 13-month old infants [15], and disrupted patterns of cortisol activity have also been seen in male children with PAE, but not

females [16]. Males, therefore, may be at higher risk of cortisol-mediated abnormalities caused by PAE than females. Studies looking at the impact of trauma in children with and without PAE revealed that children with PAE and postnatal traumatic experiences had lower intelligence scores and more severe neurodevelopmental deficits in language, memory, visual processing, motor skills and attention then those without PAE [17]. As well, greater oppositional/defiant behaviour, inattention, hyperactivity, impulsivity and social problems were also seen in the children with PAE and traumatic experiences. Taken together these findings suggest that PAE affects the development of infant and child stress systems, and these effects may differ between males and females.

Regardless of family history, people who have experienced high degrees of adversity prior to age 16 also experience a constellation of changes including reduced cortisol and heart rate reactivity, diminished cognitive capacity and unstable regulation of affect leading in some cases to behavioural impulsivity or antisocial tendencies [18]. These physiological, cognitive and affective tendencies are consistent with changes in brain function and may lead to a higher risk of developing impulsive and risky behaviours. Thus, PAE may have an additive effect in situations of pre- and postnatal stress.

It is clear from the research that PAE causes persistent changes to normal stress pathways and brain function and that these changes may lead to the development of mental health disorders. It is therefore critical for health care providers, and allied health and social service professionals, and policy makers to recognize and understand the relationship between PAE and stress, and how these interrelate to present additional challenges for individuals with FASD.

Recommendations

- 1. Implementing stress reduction, food security, and physical activity programs for women during pregnancy and the childbearing period may be an efficient strategy to counteract the impact of maternal stress on the developing fetus. Such interventions could contribute to the prevention of neurodevelopmental and mental health issues for both mothers and children. Inclusion of partners, families, and other natural supports are crucial for enhancing the effectiveness of these interventions.
- 2. PAE and childhood traumatic experiences correlate with specific behavioural problems that require the development of new approaches to meet the needs of this vulnerable group. Targeting vulnerable groups to provide postnatal support is essential to reducing the occurrence of childhood traumatic experiences. Specific training and education to equip healthcare and social service providers with tools and strategies are needed to help meet the complex needs of people living with FASD and those who support them. For example, the recommendation to communicate mental health concerns as another possible part of the FASD disability as opposed to a preventable

- consequence of poor or lacking supports provided by the family or social services.
- 3. The integration of childhood maltreatment, cortisol abnormalities and changes to brain structures need to be further studied to develop a better understanding of how the contribution of PAE and other life stressors can further impact child and family development. Specific funding opportunities to further elucidate these relationships could inform innovative programs that can address the impact of stress during development.

References

- 1. Doom, J.R. and M.R. Gunnar, *Stress physiology and developmental psychopathology: past, present, and future.* Dev Psychopathol, 2013. **25**(4 Pt 2): p. 1359-73.
- 2. Mello, A.F., et al., *Update on stress and depression: the role of the hypothalamic-pituitary-adrenal (HPA) axis.* Rev Bras Psiquiatr, 2003. **25**(4): p. 231-8.
- 3. Babenko, O., I. Kovalchuk, and G.A. Metz, *Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health.* Neurosci Biobehav Rev, 2015. **48C**: p. 70-91.
- 4. Marques, A.H., et al., *Maternal stress, nutrition and physical activity: Impact on immune function, CNS development and psychopathology.* Brain Res, 2014.
- 5. Enlow, M.B., et al., *Interpersonal trauma exposure and cognitive development in children to age 8 years: a longitudinal study.* J Epidemiol Community Health, 2012. **66**(11): p. 1005-10.
- 6. Hellemans, K.G., et al., *Prenatal alcohol exposure: fetal programming and later life vulnerability to stress, depression and anxiety disorders.* Neurosci Biobehav Rev, 2010. **34**(6): p. 791-807.
- 7. Comeau, W.L., C.A. Winstanley, and J. Weinberg, *Prenatal alcohol exposure and adolescent stress unmasking persistent attentional deficits in rats.* Eur J Neurosci, 2014. **40**(7): p. 3078-95.
- 8. Uban, K.A., et al., *Basal regulation of HPA and dopamine systems is altered differentially in males and females by prenatal alcohol exposure and chronic variable stress.*Psychoneuroendocrinology, 2013. **38**(10): p. 1953-66.
- 9. Uban, K.A., et al., Amphetamine sensitization and cross-sensitization with acute restraint stress: impact of prenatal alcohol exposure in male and female rats. Psychopharmacology (Berl), 2014.
- 10. Hellemans, K.G., et al., *Prenatal alcohol exposure and chronic mild stress differentially alter depressive- and anxiety-like behaviors in male and female offspring.* Alcohol Clin Exp Res, 2010. **34**(4): p. 633-45.
- 11. Hellemans, K.G., et al., *Prenatal alcohol exposure increases vulnerability to stress and anxiety-like disorders in adulthood.* Ann N Y Acad Sci, 2008. **1144**: p. 154-75.
- 12. Raineki, C., et al., *Neurocircuitry underlying stress and emotional regulation in animals prenatally exposed to alcohol and subjected to chronic mild stress in adulthood.* Front Endocrinol (Lausanne), 2014. **5**: p. 5.
- Haley, D.W., N.S. Handmaker, and J. Lowe, *Infant stress reactivity and prenatal alcohol exposure*. Alcohol Clin.Exp.Res., 2006. **30**(12): p. 2055-2064.
- 14. Oberlander, T.F., et al., *Prenatal alcohol exposure alters biobehavioral reactivity to pain in newborns*. Alcohol Clin.Exp.Res., 2010. **34**(4): p. 681-692.
- 15. Jacobson, S.W., J.T. Bihun, and L.M. Chiodo, *Effects of prenatal alcohol and cocaine exposure on infant cortisol levels*. Dev Psychopathol., 1999. **11**(2): p. 195-208.
- 16. Ouellet-Morin, I., et al., *Prenatal alcohol exposure and cortisol activity in 19-month-old toddlers:* an investigation of the moderating effects of sex and testosterone. Psychopharmacology (Berl), 2011. **214**(1): p. 297-307.
- 17. Henry, J., M. Sloane, and C. Black-Pond, *Neurobiology and neurodevelopmental impact of childhood traumatic stress and prenatal alcohol exposure*. Lang Speech Hear Serv Sch, 2007. **38**(2): p. 99-108.
- 18. Lovallo, W.R., Early life adversity reduces stress reactivity and enhances impulsive behavior: implications for health behaviors. Int J Psychophysiol, 2013. **90**(1): p. 8-16.