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Neuroendocrine and immune pathways from pre- and perinatal stress to substance abuse

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ABSTRACT

Early life adversity is a documented risk factor for substance abuse and addiction. The pre- and perinatal period (i.e., from implantation, through pregnancy, to 6 months of age) is a critical period marked by high biological plasticity and vulnerability, making perinatal stress a particularly robust form of adversity. The neuroendocrine and immune systems are key mechanisms implicated in the transmission of addiction risk. We review animal and human studies that provide preliminary evidence for links between perinatal stress, neuroendocrine and immune dysregulation, and risk for substance abuse and addiction. *A translational neuroscience* perspective is employed to elucidate pre- and perinatally-induced biological mechanisms linked to addiction and discuss implications for prevention and intervention efforts. Significant evidence supports associations between pre- and perinatal stress and dysregulation of the hypothalamic-pituitary-adrenal axis and immune systems as well as links between neuroendocrine/immune functioning and addiction risk. More work is needed to explicitly examine the interplay between pre- and perinatal stress and neuroendocrine/immune disruptions that together heighten substance abuse risk. Future work is needed to fully understand how pre- and perinatal stress induces biological alterations to predispose individuals to higher risk for addiction. Such knowledge will strengthen theoretically-driven and empirically-supported prevention efforts for substance abuse and addiction.

1. Neuroendocrine and immune pathways from pre- and perinatal stress to substance abuse

Approximately 21 million United States adults suffer from a substance use disorder (SUD), making substance abuse and addiction among the most urgent and costly public health problems (US Department of Health and Human Services, Office of the Surgeon General, 2016). Delineating the underlying factors that contribute to SUDs and addiction is key to mitigating the impact of addiction on individuals and communities. Early life stress is a well-documented risk factor for drug and alcohol abuse and addiction (Enoch, 2011; Stone et al., 2012). As such, elucidating the underlying neurobiological mechanisms linking early life stress and substance abuse has potential to inform and optimize prevention and treatment strategies.

The effects of stress on later health-risking behavior can begin as early as the pre- and perinatal period (i.e., from implantation, through pregnancy, to 6 months of age), a critical period of rapid fetal brain development marked by high biological plasticity and vulnerability (Lupien et al., 2009; Provençal and Binder, 2015). A complex cycle of intergenerational transmission exists, in which mothers with substance-use problems, having themselves experienced higher rates of childhood abuse, neglect, and prenatal substance exposure, are more likely to expose their offspring to similar stressors during the pre/perinatal period than mothers without substance-use problems. This cycle contributes to risk for developing substance addiction issues later in life (Cash and Wilke, 2003). Through translational neuroscience, animal and human studies have begun to establish how early forms of adversity become "biologically embedded," providing insight into mechanistic pathways that link pre/perinatal stress to future maladaptive outcomes, such as substance abuse and addiction (Miller et al., 2011). Notably, the neuroendocrine and immune systems are believed to be key mechanisms in the transmission of addiction and psychopathology risk related to acute and chronic stressors during the pre- and perinatal period (Enoch, 2011; Koob and Le Moal, 2001; Mayes and Suchman, 2006). Extant etiological models for substance abuse and addiction have limited focus thus far on the earliest developmental stages (Eiden et al., 2016), in which endocrine and immune processes may serve as potential mechanisms for future addiction-related risk. A proposed conceptual model details how pre- and perinatal stress may confer risk for addiction vulnerability through neuroendocrine and immune pathways (see Fig. 1).

This review synthesizes animal and human literature to implicate

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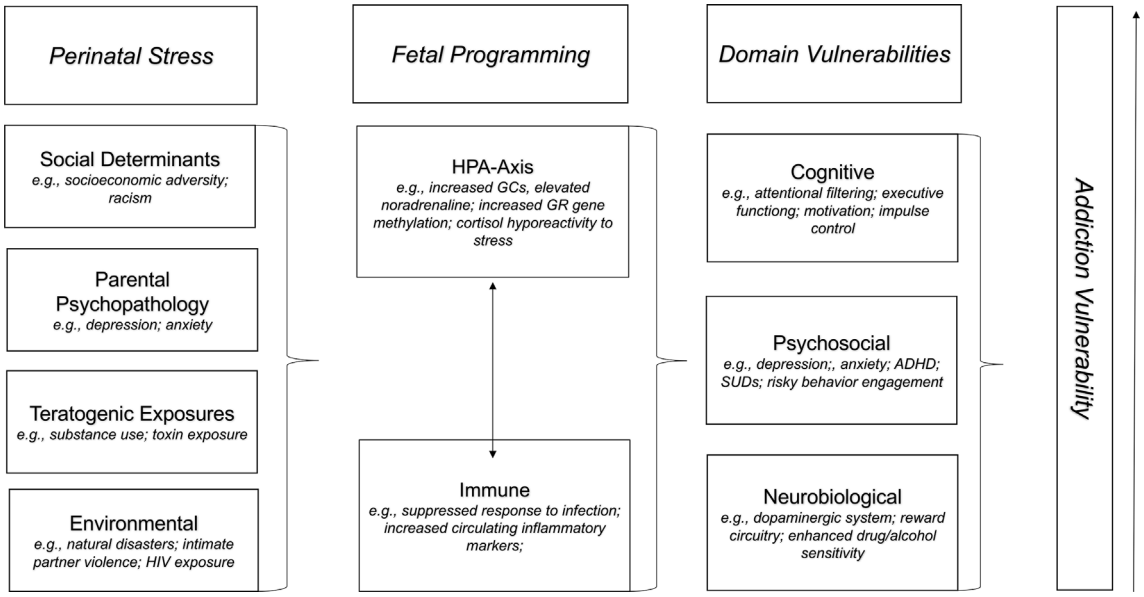

Fig. 1. Conceptual model of neuroendocrine and immune pathways from perinatal stress to addiction vulnerability.

how exposure to stress during gestation and infancy impacts neuroendocrine and immune pathways to confer risk for substance abuse and addiction. First, we review animal and human studies on three broad categories of prenatal stress: maternal stress (e.g., psychosocial stress, psychopathology), stress in the context of laboratory studies of glucocorticoid administration, and stress arising from prenatal substance exposure. In these sections, we integrate evidence on the role of the hypothalamic-pituitary-adrenal (HPA) axis. We then transition to review links between pre- and perinatal stress, offspring substance use, and immune system function. This includes a review of relevant animal studies on immune activation, viral infection, and prenatal drug administration. We then discuss links between stress, prenatal drug use, and inflammation in human studies. We include a brief section on the role of perinatal human immunodeficiency virus (HIV) exposure as a naturalistic window to understanding immune-related stressors on vulnerability to substance misuse in offspring. For each section, we first review links between pre- and perinatal stressors and substance abuse vulnerability. We then review literature on the role of the HPA-axis or immune system in these pathways. Due to the limited extant literature on these topics, stressor types have been grouped together. Further, a comprehensive review of the entire literature on each substance was outside the scope of the present paper. Table 1 includes definitions of the most common type of animal stress paradigms with their corresponding human analog.

Throughout the review, we employ a *translational neuroscience* perspective on the problem of intergenerational transmission of substance use and addiction. This perspective encourages a nuanced understanding of how these pathways link stress during early developmental stages to substance abuse across the lifespan (Fisher and Berkman, 2015). Specifically, translational neuroscience aims to pinpoint causal and moderating biological factors with the goal of leveraging this knowledge to the optimization of prevention and intervention strategies (Fisher and Berkman, 2015). The objective of translational neuroscience research is to not only to elucidate the multitudinous impacts of early life stress on these individual mechanisms that confers risk for substance abuse, but also to examine the interplay amongst them. We close by discussing implications for prevention and intervention strategies for addiction.

1.1. Early experiences, the HPA axis, and pathways to substance abuse

Due the semi-permeable nature of the placenta, high levels of maternal stress and associated physiological alterations in neuroendocrine and immune systems produce changes in the fetal environment (Barrett et al., 2017). This process is referred to as fetal programming (Glover et al., 2010; Kapoor et al., 2008). While fetal programming can be detrimental in many modern contexts, it may have served a useful purpose earlier in human evolutionary history, such as resource conservation in harsh environments (Seckl and Holmes, 2007). Stress effects via fetal programming are considered a conduit for children's later vulnerability to a range of mental and physical health detriments, including substance abuse and addiction. One of the primary factors underlying the pathway from fetal development to adult-onset disorders are glucocorticoids (GCs), cortisol in humans, which are key mechanisms of HPA axis programming (Davis and Sandman, 2010). Glucocorticoids are a particularly potent chemical signal due to their far-reaching impacts across every major regulatory system (e.g., immune, gut, autonomic nervous system, neural) (McEwen, 2013). Animal models have illustrated that the neuroendocrine and immune effects of profound stress are principally mediated through GC pathways

Table 1
Examples of animal models of pre- and perinatal stress and human analogs.

Name	Description	Human Analog
Prenatal substance exposure	Injection of substance (e.g., cocaine, morphine) into mother	Prenatal substance exposure
Synthetic GC exposure	Injection of synthetic glucocorticoid into mother	Glucocorticoid use during pregnancy
Food restriction paradigm	Restrict mother access to food	Malnutrition
Restraint and immobilization stress paradigm	Mother kept in cylindrical tube or restrained with adhesive tape	Prenatal anxiety
Immune activation	synthetic double strand RNA polyriboinosinic-polyribocytidilic acid (poly I:C) administered into mother	Prenatal viral infection
Maternal separation	Offspring exposed to maternal absence during first postnatal weeks	Postnatal neglect