Brigham and Women's Hospital

Theme: Fetal antecedents to sex differences in depression: a translational approach

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Abstract

Major depressive disorder (MOD) is the fourth leading causes of morbidity and mortality world-wide, with women having twice the incidence than men. We are proposing a translational SCOR to integrate scientists from basic, clinical neuroscience and population-level perspectives to address the question of why women are at higher risk for MOD than men. Our underlying premise is that sex differences in adult MOD are initiated during mid-gestation, a period of Hypothalamic-Pituitary-Adrenal axis (HPA) circuitry development, sexual differentiation of the brain, and a period in which fetal risk factors for MOD have been identified. We will test hypotheses regarding the roles of adrenal and gonadal signaling pathways regulating BDNF and its interactions with GABA-ergic, GLU-tamatergic, and nitric oxide (NO) mechanisms in the development of regions in stress response circuitry. Project 1, a human in-vivo study of 500 DSM-IV MOD cases and 500 normal controls from a birth cohort (followed from prenatal development to age 47) will test for genetic polymorphisms associated with these pathways and maternal serum assessment of HPA abnormalities during mid-gestation to understanding sex differences in MOD. 40 recurrent cases matched to 40 normal controls will be re-recruited for functional brain imaging of stress response circuitry and neuroendocrine evaluations to test our hypotheses relating abnormal maternal-fetal HPA environment and genetic polymorphisms with sex differences in adult HPA dysfunction and stress response circuitry deficits. Project 2 consists of mouse models of developmental morphology and adult behavior regarding genetic and/or hormonal sex differences in embryonic HPA circuitry neurogenesis, cell migration, and cell death and the impact of these hormones and/or genes on sex differences in adult MOD phenotypic behavior analogous to human studies. Project 3 uses rat models to study morphological and adult endocrine outcomes, after fetal and neonatal glucocorticoid treatment on sex differences in developing HPA circuitry and adult sex differences in hormonal dysregulation and MOD phenotypic behavior. This includes the role of epigenetic factors

resulting from early adverse glucocorticoid exposure. Our interdisciplinary team of senior preclinical and clinical investigators, who collaborate with each other, have spent their careers studying the roles of hormones and genes in understanding sex differences in the brain, neuroendocrine deficits, and/or the treatment of MOD. To accomplish the integration of SCOR projects, we propose an Administrative Core. Thus the SCOR would provide support to formalize our collaborations to focus on a problem of major public health significance that has etiologic implications, particularly for women, and will provide knowledge for development of sex-specific treatment and prevention strategies.

Project 1: Genes and Hormonal Fetal Antecedents to Sex Differences in the Brain: Depression
Type: Clinical

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Major depressive disorder (MOD) is the fourth leading cause of disease burden worldwide, and the incidence of MOD in women is twice that of men. Thus understanding its etiology will have important implications for attenuation of disease burden, particularly in women. In this translational SCOR integrating scientists from basic and clinical fields in three Projects, we address the question of why women are at twice the risk for MOD than men. We hypothesize that sex differences in MOD are initiated during fetal development, during hypothalamic-pituitary-adrenal (HPA) circuitry development and the sexual differentiation of the brain, and a period in which fetal risk factors for MOD have been identified. The overall SCOR will test hypotheses regarding the roles of adrenal and gonadal signaling pathways regulating brain-derived nerve growth factor (BDNF; associated with MOD) and its interactions with gamma aminobutyric acid (GABA)-ergic, glutamate (GLU)-tamatergic and nitric oxide (NO) mechanisms in development of key brain regions in stress response circuitry. In Project 1, specific aims are to test for contributions of genetic polymorphisms associated with these pathways and maternal serum assessment of HPA abnormalities during mid-gestation to understanding sex differences in MOD. We identified 500 DSM-IV MOD cases and 500 normal controls from a birth cohort (followed from prenatal development to age 47) in which DMA has been stored and biosamples indicating maternal-fetal HPA-placental stress at mid-gestation will be evaluated. We will test for specific genetic polymorphisms associated with HPA circuitry development and MOD (cortiocotropin releasing hormone (CRH), BDNF, GABA, GLU, neuronal NO (nNOS), estrogen receptors (ER)a and p, and arginine vasopressin (AVP)). Mid-gestational physiologic stress will be operationalized as: abnormal levels of maternal-fetal hormones during mid-gestation indicative of stress (CRH, dehydroepiandrosterone-sulfate (DHEA-S), human chorionic gonadotropin (hCG), and bioactive androgens); and high levels of proinflammatory cytokines (interleukine (IL)-1p, IL-6 & tumor necrosis factor (TNF)-a) during

mid-gestation. In addition 40 recurrent MOD cases, equally divided by gender, and 40 individually-matched normal controls from this birth cohort will be re-recruited for functional and structural brain imaging of stress response circuitry and neuroendocrine evaluations to test our hypotheses relating abnormal maternal-fetal HPA environment and genetic polymorphisms with sex differences in adult HPA axis dysfunction and functional brain activity deficits in stress response circuitry. We predict hormonal dysfunction will mediate sex differences in brain activity deficits in MOD, which will be associated with maternal-fetal HPA abnormalities. An understanding of the fetal mechanisms associated with sex differences in MOD will have etiologic imolications and imoortance for the development of sex-specific treatments and prevention of MOD.

Project 2: Animal Models of Sex-Specific HPA Axis Development
Type: Basic

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Abstract

The work being performed in this subcontract references the study named above. The proposed work for this subcontract to conduct Project 2 will focus on the paraventricular nucleus of the hypothalamus (PVN) as the key final common integration site and output pathway of the HPA axis. The proposed aims will test hypotheses for facets of PVN development as they may contribute as fetal antecedents to adult dysfunction that may include susceptibility to major depressive disorder (MDD). Nuclear development proceeds through several key developmental phases that can be characterized simply by the generation of neurons, the migration of neurons to proper positions, the choice of life or death for new neurons, the establishment of cell phenotypes, and finally the establishment of functional connections. Using mouse models and knock-out gene strategies, Project 2 aims will test hypotheses for each of these facets of PVN development as they may contribute as fetal antecedents to adult dysfunction that may include susceptibility to MDD.

Project 3: Sex-Specific Programming of the HPA Axis by Glucocorticoids
Type: Basic

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Abstract

The work being performed in this subcontract references the study named above. The proposed work for this subcontract will focus on specific hypotheses on the long-term consequences of fetal/neonatal glucocorticoid exposure on the developing hypothalamo-pituitary-adrenal (HPA) axis, which may have significant implications for understanding sex differences in major depressive disorder (MOD) investigated in Project 1. Project 3 animal investigations in a rat model will test the following aims. Aim 1) Developmental exposure to glucocorticoids causes permanent changes in the function of the HPA axis by increasing the incidence of death in a select neuronal phenotype in brain areas controlling hormonal and behavioral responses to stress, or by causing permanent alterations in gene expression in neurons in these brain areas through DNA methylation events. Aim 2) There are sex-specific effects of perinatal glucocorticoid exposure on the developing HPA axis, as a result of molecular interactions between glucocorticoid and estrogen receptors.

CORES

Administrative Core

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Abstract

Major depressive disorder (MOD) is the fourth leading causes of morbidity and mortality world-wide, with women having twice the incidence than men. Thus, understanding sex differences in MOD will have important implications for public health and development of sex-specific treatment strategies to alleviate disability and ultimately for prevention. We are proposing a translational SCOR to integrate scientists from basic, clinical neuroscience and population-level perspectives to address the question of why women are at higher risk for MOD than men. An underlying premise is that sex differences in MOD are initiated during fetal development. We propose a unique design in which we will integrate findings from three studies (human in vivo and two animal model studies) to investigate hypotheses regarding how adverse maternal-fetal hypothalamic pituitary adrenal (HPA) programming during mid-gestation and genetic polymorphisms will disrupt normal HPA circuitry development in the context of the sexual differentiation of the brain and thereby have important implications for understanding the vulnerability for sex differences in MOD in adult brain abnormalities and endocrine dysfunction. To accomplish the integration of our diverse group of investigators, the Administrative Core will provide an infrastructure to accomplish our goals, under the direction of the PI, Co-Pi and administrative staff. The aims of this Core are the following: 1) To coordinate the activities of

the SCOR, e.g. provide logistical support, such as setting up meetings and conference calls, monitoring ongoing operational issues, and maintaining connections with the Scientific Advisory Board; 2) To administer budgets, e.g. monitor financial expenditures and insure fiscal responsibilities; 3) To disseminate knowledge, e.g. coordinate publications, develop a website, organize conferences, publicize opportunities for trainees. The SCOR provides an excellent mechanism for the proposed projects, since they are a set of inextricably linked interdisciplinary studies focused on the identification of mechanisms involved in understanding sex differences in MDD. Given the complexities of conducting cross-institution and cross-discipline studies, it is important to have an administrative infrastructure to "bind" and monitor ongoing activities, provide fiscal administration for the SCOR as a whole, and be a vehicle for dissemination of knowledge resulting from the SCOR to the scientific and medical communities, policy makers, and the public.