Title
34.1 GENETIC MUTATIONS AND ENVIRONMENTAL FACTORS THAT PROMOTE ADVERSE NEURODEVELOPMENTAL OUTCOMES IN PRECLINICAL MODELS

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Methods: Model systems can be used with a variety of approaches that shed light on several important questions: 1) What are the roles that gene variants identified in children and adolescents with mental health disorders play in the nervous system? 2) How do known risk factors for childhood and adolescent mental health disorders affect brain development and functioning? 3) How do neural systems identified in animals inform the development of treatments?

Results: This Symposium briefly reviews past work in animal model systems that have advanced the field and presents on 4 significant areas of ongoing work: 1) genetic and environmental factors that promote adverse neurodevelopmental outcomes in preclinical models, 2) dopamine D4 receptors and nicotine exposure in animal models of neurodevelopmental disorders, 3) use of animal models to study effects of prenatal alcohol exposure on neurodevelopment; and 4) use of animal models to study cerebellar functions relevant to human mental health disorders.

Conclusions: The ultimate goal of all of these areas of investigation is to more deeply understand the underpinnings of mental health disorders to improve outcomes in children and adolescents by developing better diagnosis, prevention, and treatment. ANI, NEURODEV, R

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34.1 GENETIC MUTATIONS AND ENVIRONMENTAL FACTORS THAT PROMOTE ADVERSE NEURODEVELOPMENTAL OUTCOMES IN PRECLINICAL MODELS
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Objectives: Developmental exposure to environmental neurotoxicants, such as polychlorinated biphenyls (PCBs), is implicated in the pathogenesis of neurodevelopmental disorders (NDDs). Mechanistic studies have shown that PCBs alter calcium-dependent signaling pathways linked to activity-dependent dendritic growth. Mutations in calcium signaling molecules are associated with increased NDD risk, so we are using mouse models to test the hypothesis that heritable mutations that alter the fidelity of calcium signals influence neurodevelopmental outcomes after developmental PCB exposure.

Methods: Mice expressing a human ryanodine receptor gain-of-function mutation (T4826I), X-linked FMR1 CGG repeat expansion (170–200 repeats; CGG), or both mutations (double mutation, DM) and congenic wild type (WT) mice were exposed throughout gestation and lactation to a PCB mixture in drinking water. The mixture mimulates the PCB congener profile in the serum of women at an increased risk for having a child with an NDD. Dendritic arborization, repetitive behavior, and sociability were measured in pups.

Results: PCBs and genetic mutations independently alter dendritic morphology, generally increasing complexity. Genotype modulates the impact of PCBs on dendritic morphology in a sex-, dose-, and brain region-dependent manner (eg, male cortical neurons from T4826I and DM are more sensitive than WT to the dendritic effects of PCBs). Genotype alone influences behavior. Compared with WT mice, T4826I, CGG, and DM mice emit fewer ultrasonic vocalizations, T4826I and DM mice spend more time grooming, and DM mice fail to display sociability. PCBs phenocopy some of these effects in WT mice. D4.7 variant of DRD4 is associated with the elevated risk for ADHD, especially when there has been prenatal exposure to maternal smoking. Studies of animal species suggest that certain environmental exposures can lead to ADHD-like phenotypes (especially in males). In some cases, changes in D4 receptor expression or function have been implicated as part of the underlying mechanism producing ADHD-like behaviors. DRD4-humanized mice expressing D4.4 or D4.7 receptors show some ADHD-related behavioral differences compared with wild-type (WT) mice, and there is preliminary evidence of sex-specific ADHD-related behavior changes in D4.7/WT mice after nicotine exposure.

Conclusions: Studies of multiple animal species suggest that genetic and environmental factors affecting D4 receptor expression and/or function may contribute to neurodevelopmental and behavioral phenotypes. DRD4-humanized mice are being used to study the mechanisms underlying genetic and environmental influences on ADHD-related behaviors and other neurodevelopmental phenotypes. Understanding these mechanisms may lead to improved prevention and treatment of neurodevelopmental disorders in humans.

ND, ANI, NECHEM

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34.2 DOPAMINE D4 RECEPTORS IN ANIMAL MODELS OF NEURODEVELOPMENTAL DISORDERS
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Objectives: Previous research suggests that the exon 3 variable number of tandem repeat (VNTR) polymorphism of the human dopamine D4 receptor gene (DRD4) contributes to ADHD and other psychiatric phenotypes. Animal studies may show how differences in D4 expression and function lead to these phenotypes and whether environmental factors influence behavioral outcomes.

Methods: This presentation discusses D4 receptor function in multiple species, with an emphasis on differences in neurodevelopment, behavior, brain function, and response to environmental exposures, depending on the genotype. Relevant studies of zebrafish, rodents, and lizards briefly are reviewed, but the main focus is on the development of humanized DRD4 mouse models using homologous recombination to knock out the mouse gene and insert human D4 variants.

Results: In humans, the D4.7 variant of DRD4 is associated with the elevated risk for ADHD, especially when there has been prenatal exposure to maternal smoking. Studies of animal species suggest that certain environmental exposures can lead to ADHD-like phenotypes (especially in males). In some cases, changes in D4 receptor expression or function have been implicated as part of the underlying mechanism producing ADHD-like behaviors. DRD4-humanized mice expressing D4.4 or D4.7 receptors show some ADHD-relevant behavioral differences compared with wild-type (WT) mice, and there is preliminary evidence of sex-specific ADHD-relevant behavior changes in D4.7/WT mice after nicotine exposure.

Conclusions: Studies of multiple animal species suggest that genetic and environmental factors affecting D4 receptor expression and/or function may contribute to neurodevelopmental and behavioral phenotypes. DRD4-humanized mice are being used to study the mechanisms underlying genetic and environmental influences on ADHD-related behaviors and other neurodevelopmental phenotypes. Understanding these mechanisms may lead to improved prevention and treatment of neurodevelopmental disorders in humans.

ND, ANI, NECHEM

34.3 EFFECTS OF THIRD-TRIMESTER EQUIVALENT ETHANOL EXPOSURE ON NEURODEVELOPMENTAL GENE EXPRESSION
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Objectives: Third-trimester alcohol exposure has profound effects on neurodevelopmental gene expression, especially in brain regions that develop in late gestation such as the prefrontal cortex (PFC). Ethanol (EtOH) induces polyADP-ribose polymerase (PARP) enzymatic activity in cell and animal models, which reportedly participates in S-methylcytosine (SmC) and S-hydroxymethylcytosine (SmHC) removal. We hypothesized that EtOH increases PARP activity, inducing its DNA demethylation activity, leading to increased expression of genes involved in neuronal development and cellular differentiation.

Methods: Male rat pups were treated with 5.25 g/kg per day EtOH, the PARP inhibitor ABT-888 (25 mg/kg per day), or a combination of the 2 via intragastric intubation during postnatal days (PD) 4–9, which in rats is analogous to the third trimester of human pregnancy. RNA-seq, quantitative reverse transcription-polymerase chain reaction (PCR), or PARP enzymatic activity assays were

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