Animal Models and Novel Insights into the Neurobiology of ADHD

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Prenatal Nicotine Exposure Mouse Model of ADHD

• Prenatal nicotine exposure is a significant risk factor for ADHD (Construct Validity)
• The mouse model shows behavioral, neurochemical and neuro-anatomical changes similar to those seen in ADHD (Face Validity)
• Stimulants ameliorate the ADHD-like phenotypes in the mouse model (Predictive Validity)
New Insights into Mechanism of Stimulant Abuse/Addiction

- In the mouse model, therapeutic equivalent doses of methylphenidate activate the dopaminergic system, and
- Supra-therapeutic doses activate the opioid system
- Thus, a potential mechanism mediating stimulant abuse becomes evident
New Insights into Mechanism of Stimulant Abuse/Addiction

• Opioid receptor antagonist mitigates the abuse potential of methylphenidate in the mouse model
• Clinical studies confirm the data from the mouse model
• These findings could lead to development of abuse deterrent methylphenidate formulations
New Insights into Neurobiological Mechanisms of ADHD

• In the mouse model, ADHD-like phenotypes produced by nicotine exposure are not only limited to the nicotine-exposed individual, but also are transmitted to generations descending from that individual.

• The trans-generational transmission occurs when the mother or the father is exposed to nicotine.
New Insights into Neurobiological Mechanisms of ADHD

• Nicotine exposure of the father leads to ADHD-like phenotypes in the offspring in at least 2 generations. The offspring display
  1. Hyperactivity
  2. Attention deficit
  3. Cognitive Inflexibility
New Insights into Neurobiological Mechanisms of ADHD

• Transgenerational transmission of ADHD-like phenotypes from the father to his descendants is associated with

  1. Epigenetic changes in the DNA of germ cells of the nicotine-exposed father

  2. Changes in gene expression in the brains of the offspring

  3. Changes in dopamine content in the brains of the offspring
Animal Models and Novel Insights into the Neurobiology of ADHD

• Animal models play a critical role in the identification of:
  o Mechanism of action of ADHD drugs
  o Molecular targets for drug discovery and development
  o Neurobiological mechanisms of ADHD and its transgenerational transmission