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2. Title
   Molecular and Neural Bases Underlying ADHD-Like Phenotypes in Offspring of Sire Mice Chronically Exposed to Nicotine

3. Period
   2022-2024

4. Summary
   It has been suggested that long-term paternal smoking may increase the risk of mental disorders such as attention deficit/hyperactivity disorder (ADHD) in offspring; however, the molecular mechanisms underlying this phenomenon remain unclear. On the other hand, paternal experiences can alter the epigenome of germ cells and influence the behavior of offspring. However, how long-term paternal smoking affects germ cells and subsequently alters the offspring's neurodevelopment remains unknown. In this study, we examined whether offspring derived from male mice chronically exposed to nicotine-a major component of tobacco-exhibited ADHD-like behaviors. The results showed that the offspring of nicotine-exposed sire displayed ADHD-like behaviors, which were ameliorated by atomoxetine, a norepinephrine transporter inhibitor used in the treatment of ADHD. Next, we investigated the norepinephrine (NA) system in the brain of offspring. Chronic paternal nicotine exposure led to a reduction in the number of NA neurons in the locus coeruleus, a decrease in NA nerve terminals in the prefrontal cortex (a projection target), and abnormalities in NA neurotransmission. Taken together, long-term paternal smoking (nicotine intake) induces abnormalities in the NA system of offspring, which may contribute to the development of ADHD-like behaviors.