Paternal exposure to cigarette smoke toxicants causes adverse developmental, neurological, and behavioral outcomes in the offspring

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Paternal exposure to cigarette smoke has been strongly implicated in several birth defects and childhood cancers even though the mechanism behind these paternally mediated developmental outcomes is unknown. Cigarette smoke causes deleterious consequences mostly through its 7000 chemical constituents and 70 proven carcinogens. We developed a mouse model in which the epididymal sperm of sire exposed to cigarette smoke condensate (CSC) for 40 consecutive days had higher levels of **10** miRNAs. Q-RTPCR analysis of offspring brains at e18.5 detected upregulation of these candidate miRNAs when the dams were mated with the males within one week of cessation of CSC exposure. The expression of the candidate miRNAs namely, miR-9-5p, miR-30a-5p, miR-34b-3p, miR-122-5p, miR-338-5p, and miR-494-3p in the exposed sire sperm showed a strong indirect correlation with their putative targets such as *Drd2, Grin2a, Scn8a, Adra2a, Ahr, Slc2a13, Ahr, Slc25a34, Slc1a5, Rad50,* and *Chrna5* in fetal F1 brains. The expression of receptors involved in striatal neural circuitry such as alpha-2A adrenergic receptor (*Adra2a*), dopamine receptors (DRD2 and DRD4), glutamate ionotropic receptor 2A sub-unit (Grin2a), nicotinic acetylcholine receptors (*Chrna3* and *Chrna5*), and genes implicated in Alzheimer's disease (*App*, and *Psen1*) demonstrated a steady increase in the F1 (e18.5) fetal brains. Western blot analysis of the e18.5 fetal brain of delayed mating group detected increase in DRD1, DRD2, and ADRA1A and decrease in GRIA2 (glutamate ionotropic receptor AMPA type subunit 2 / AMPAR), and GRIN1 (glutamate ionotropic receptor NMDA type subunit 1 / NMDAR1). In addition to decreased body weight and size, and higher rate of embryo resorption, the progeny of the CSC-exposed sire revealed faster motor response, higher anxiety, and reduced startle response or auditory. These data suggest that the paternal CSC exposure mediates the developmental defects, and behavioral changes in the offspring through the altered expression of sperm-borne miRNAs.