1. No.
   2022G030

2. Title
   Nicotine-Induced Estrogenic Action on Cognitive Brain Function

3. Period
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4. Summary

Sex differences in smoking effects are partly due to nicotine-inducible estrogen production. In the present study, we aimed to understand the brain mechanisms of the estrogenic regulation of the nicotine-inducible behavioral changes. Both sexes of adult ERβ-RFP^{tg} mice (in which estrogen receptor beta is tagged with red fluorescent protein) were subcutaneously implanted with an osmotic mini pump filled with four different doses of nicotine (nicotine hydrogen tartrate salt) dissolved in saline. They were then tested for four different behavioral paradigms, *i.e.*, light-dark transition, social interaction, open-field, and home-cage running wheel activity tests, during the following 28 days. Nicotine treatment most profoundly affected social behavior toward an unfamiliar stranger mouse in both sexes of mice in a sex-specific manner. In female mice, nicotine treatment at the highest dose of 10 μg/μl decreased the total duration of sniffing toward a cylinder with a female stimulus mouse, suggesting an enhancement of social anxiety. On the other hand, male mice in the nicotine-treated groups at the doses of 10 and 20 μg/μl showed a significantly longer sniffing duration towards a male stimulus mouse compared to the saline control group, suggesting potentiation of social interests and arousal. We also measured mRNA levels of estrogen receptor alpha (ERα) and beta (ERβ) as well as aromatase expression in three different brain blocks (dorsal and ventral hippocampus and hypothalamus) collected upon the completion of behavioral studies. It was found that ERα and aromatase levels in the hypothalamus were significantly lower in the nicotine-treated group at the dose of 10 μg/μl compared to the saline control group in female mice (for which so far the analysis has been completed). Based on these findings, we have concluded that it is necessary to further delineate the causal relationship between nicotine-inducible social behavioral changes and ERs/aromatase expression in various brain regions in both sexes of mice, including those exposed to nicotine during the perinatal period.