Gender differences in the effect of acute nicotine administration in rat brain by MRS.

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Purpose

There are strong gender differences in developing of smoking addiction and the risk of disorders during cessation. Women appear less able to stop smoking and are more likely to experience depression during smoking cessation [1]. Very little is known about the underlying mechanisms of such differences and there is a lack of available biomarkers of smoking addiction. In this study we utilized MRS to establish the gender differences in acute reaction to nicotine administration.

Materials and Methods

Twenty four Sprague-Dawley rats (N = 12 of each gender, 60 days old, 364 ± 80 g males and 255 ± 32 g females) were used. Three animals of each gender were used as a control (single dose, 2 ml/kg saline, i.p.) and 9 were treated with nicotine tartrate (single dose, 1 mg/kg i.p). MR spectra were taken from hippocampus (HC), nucleus accumbens (NAC) and anterior cingulate cortex (ACC) using PRESS with VAPOR and OVS (TE = 8 ms, TR = 2.2 s, NA = 256) in a Bruker Biospec 7T/30USR spectrometer equipped with 12 cm gradient insert and 4-channel phased array rat brain coil. Reference spectra (without water suppression) were acquired from each region before the start of the experiment for eddy current correction and water scaling during MRS analysis using LCModel. Nicotine or saline was injected after one baseline spectrum from each region was taken and scanning continued until five more spectra from each region were acquired. Animals were anesthetized (isoflurane, 3% induction, 1-2% maintenance) and their core temperature was maintained at 37.1 ± 0.6°C using warmed circulating water during the scan. Statistical tests were performed using repeated measures ANOVA.

Results and Discussion

Baseline spectra showed statistically significant differences between genders in some metabolites (Table 1). Figure 1 shows the dynamic changes in selected metabolites during first two hours after single injection of nicotine or saline. Gender differences were found in all studied regions: HC (taurine), NAC (taurine, NAA, creatine), ACC (taurine, GABA). Female rats consistently showed lower concentrations of these neurometabolites than males after nicotine injection and in the baseline scans. There were also significant changes in GABA, glutamate, and myo-inositol in HC due to nicotine administration, but there were no gender differences (data not shown). The most dramatic changes were observed in taurine concentration, which is believed to be part of the intrinsic neuroprotective system [2]. These data suggest that there are gender differences in neurometabolic reaction of the brain to nicotine, which may be related to the brain reward circuit and glutamate cycle. MRS could serve a valuable role in the development of non-invasive biomarkers of nicotine and possibly other drugs addiction. Further studies with chronic nicotine and tobacco smoke exposure are warranted.

Table 1. Gender differences (P < 0.05) in the baseline spectra. Data are mean ± s.e.m., mM.

	males	females
GABA (HC)	2.58 ± 0.05	2.36 ± 0.06
Taurine (HC)	6.85 ± 0.21	5.82 ± 0.12
Taurine (NAC)	7.53 ± 0.13	6.43 ± 0.16
NAA (HC)	9.99 ± 0.14	9.47 ± 0.18
Creatine (HC)	8.36 ± 0.19	7.77 ± 0.13

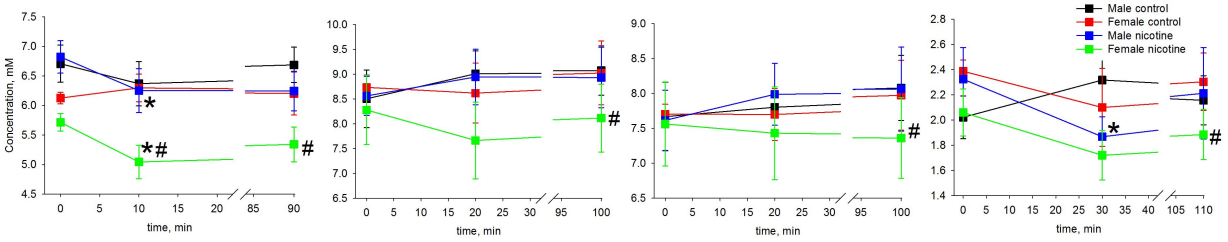

Figure 1. Dynamic changes in some neurometabolites after single injection of nicotine or saline (control). * - statistical difference with the baseline (time 0, P < 0.05), # - statistical difference between nicotine and control groups, in all figures there were statistical differences between nicotine treated male and female groups (P < 0.05, RM ANOVA).

References

1. Epperson CN, et al. Biol Psychiatry, 2005; 57: 44-48.
2. Ripps H, et al. Mol Vis, 2012; 18: 2673-86.