ROLE OF VARENICLINE ON THE VOIDING FUNCTION IN RAT

Hypothesis / aims of study
Varenicline binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors (1). Varenicline’s activity at a sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to α4β2 receptors. Varenicline binds to α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system. This prompts us to determine that does Varenicline have an effect and which neurotransmitters are involved in action mechanism of Varenicline.

Study design, materials and methods
Voiding was studied in awake female Sprague-Dawley awake rats (230±20g). Intracerebroventricular (icv) catheter (stanless-steel) was inserted to 1.0mm lateral, 0.3mm anterior, 5.3mm ventrally. Intravenous (i.v.) catheter (PE-50) was inserted to right jugular vein and intravesical catheter (PE-60) was inserted through the bladder dome. After the surgery, cystometry (CMG) was performed by infusing saline into the bladder at a constant rate (0.04 ml/min). After 2 hours, dose-response curves were constructed by administering artificial cerebro spinal fluid (aCSF) (icv), Saline (iv) and increasing dose of Varenicline [0.01-1 μg in 1μl icv; 0.01-10 μg in 200μl iv] at 1 hours intervals. The intravesical pressure to induce micturition [pressure threshold (PT)], maximal voiding pressure (MVP), and intercontraction interval (ICI) were measured. To examine action mechanism of Varenicline, administering saline intravenous. After 1 hour, Varenicline (0.1-10μg) was also administered 15 min after SCH-23390 (0.5 mg/kg, i.v.), a D1 dopamine receptor antagonist or MK-801 (0.5 mg/kg, i.v.), an NMDA antagonist i.v. injection of saline and Varenicline (0.1-10μg). The intravesical pressure to induce micturition (PT), MVP, and ICI were measured. Data are presented at means ± SEM (Standard Error of the Mean). P< 0.05 was considered statistically significant.

Results
Voiding parameters were not changed after intracerebroventricular injection of aCSF. Low doses of Varenicline (0.01, 0.1 μg) did not alter any CMG parameter, whereas a high dose (1 μg) significantly increased the ICI (control vs. Varenicline 1μg, 359.6 ± 42.8 vs. 625.8 ± 77.8 sec) (p<0.001), but did not changed MVP, PT. Voiding parameters were not changed after intravenous injection of saline. Low doses of Varenicline (0.01, 0.1 μg) did not alter any CMG parameter, whereas a high dose (1, 10 μg) significantly increased the ICI (control vs. Varenicline 1μg, 10μg, 331.6 ± 20.6 vs. 455.1 ± 49.0, 481.6 ± 46.7 sec) (p<0.001), but did not changed MVP, PT. After pre-treatment of SCH-23390 (0.5 mg/kg), intravenous injection of Varenicline 0.1-10μg did not significantly changed ICI (control v.s. Varenicline 0.1, 1, 10μg, 306.2±32.4 v.s. 275.3±3.4 , 321.6±24.4, 357.0±59.4 sec) (p>0.05), MVP, and PT (p>0.05). After pre-treatment of MK-801 (0.5 mg/kg) intravenous injection of Varenicline 0.1-10μg did not significantly changed ICI (control v.s. Varenicline 0.1, 1, 10μg, 238.5±24.9 v.s. 235.0±40.3, 243.4±38.6, 210.8±38.0 sec) (p>0.05), MVP, and PT (p>0.05).

Interpretation of results
α4β2 neuronal nicotinic acetylcholine receptor agonist/antagonist, Varenicline (1μg of icv and 1, 10μg of iv) has significantly induced increase of the ICI in the rat. D1 dopaminergic antagonist or NMDA-glutamatergic antagonist have had a partial blocking effect on inhibitory action of Varenicline in voiding reflex in the CNS.

Concluding message
These results suggest that α4β2 nicotinic acetylcholine receptors in the CNS have an effect on voiding reflex and action mechanism of α4β2 nicotinic acetylcholine receptors are mediated by various neural transmitters.

References