

## ROLE OF VARENICLINE ON THE VOIDING FUNCTION IN RAT

### Hypothesis / aims of study

Varenicline binds with high affinity and selectivity at  $\alpha 4\beta 2$  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  $\alpha 4\beta 2$  receptors. Varenicline binds to  $\alpha 4\beta 2$  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  $\alpha 4\beta 2$  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 (stainless-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  $\mu$ g in 1 $\mu$ l icv; 0.01-10  $\mu$ g in 200 $\mu$ l 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 (0.1-10 $\mu$ g) 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 (0.1-10 $\mu$ g). The intravesical pressure to induce micturition (PT), MVP, and ICI were measured. Data are presented at means  $\pm$  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  $\mu$ g) did not alter any CMG parameter, whereas a high dose (1  $\mu$ g) significantly increased the ICI (control vs. Varenicline 1 $\mu$ g, 359.6  $\pm$  42.8 vs. 625.8  $\pm$  77.8 sec) (p<0.001). but did not change MVP, PT. Voiding parameters were not changed after intravenous injection of saline. Low doses of Varenicline (0.01, 0.1  $\mu$ g) did not alter any CMG parameter, whereas a high dose (1, 10  $\mu$ g) significantly increased the ICI (control vs. Varenicline 1 $\mu$ g, 10 $\mu$ g, 331.6  $\pm$  20.6 vs. 455.1  $\pm$  49.0, 481.6  $\pm$  46.7 sec) (p<0.001), but did not change MVP, PT. After pre-treatment of SCH-23390 (0.5 mg/kg), intravenous injection of Varenicline 0.1-10 $\mu$ g did not significantly change ICI (control v.s. Varenicline 0.1, 1, 10 $\mu$ g, 306.2 $\pm$ 32.4 v.s. 275.3 $\pm$ 3.4, 321.6 $\pm$ 24.4, 357.0 $\pm$ 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 0.1-10 $\mu$ g did not significantly change ICI (control v.s. Varenicline 0.1, 1, 10 $\mu$ g, 238.5 $\pm$ 24.9 v.s. 235.0 $\pm$ 40.3, 243.4 $\pm$ 38.6, 210.8 $\pm$ 38.0 sec) (p>0.05), MVP, and PT (p>0.05).

### Interpretation of results

$\alpha 4\beta 2$  neuronal nicotinic acetylcholine receptor agonist/antagonist, Varenicline (1 $\mu$ g of icv and 1, 10 $\mu$ g 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 on voiding reflex in the CNS.

### Concluding message

These results suggest that  $\alpha 4\beta 2$  nicotinic acetylcholine receptors in the CNS have an effect on voiding reflex and action mechanism of  $\alpha 4\beta 2$  nicotinic acetylcholine receptors are mediated by various neural transmitters.

### References

1. [Biochem Pharmacol](#) (2007)74;1092-1101.

<b>Specify source of funding or grant</b>	None
<b>Is this a clinical trial?</b>	No
<b>What were the subjects in the study?</b>	ANIMAL
<b>Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?</b>	Yes
<b>Name of ethics committee</b>	Kyung Hee Medical Center Animal Research IRB