Effect of d-Nicotine on the I-Nicotine-Induced Increase in Gastric Acid Secretion in Rats

Mitsuhiro NAGATA, Toshio ISHIKAWA and Yoshitsugu OSUMI
Department of Pharmacology, Kochi Medical School, Nankoku, Kochi 781-51, Japan
Accepted December 5, 1984

Abstract—d-Nicotine (1000 μg) applied into the cerebral ventricle of urethane anesthetized rats increased gastric acid secretion. When 50 μg of d-nicotine was concomitantly administered with 5 μg of I-nicotine, the I-nicotine-induced increases in gastric secretion was blocked. The appearance of convulsion induced by I-nicotine in mice was also inhibited by pretreatment with d-nicotine. These results suggest that d-nicotine has agonistic and antagonistic actions to I-nicotine in the central nervous system and that its agonistic potency varies with preparations.

It was reported that intraventricularly applied I-nicotine produced a dose-related increase in gastric acid secretion mediated by cholinergic nicotinic receptors in the central nervous system (1, 2). On the other hand, there are two optical isomers of nicotine and data on the central and peripheral effects of the d-isomer, as compared with those of the I-isomer, have been reported (3–7).

We studied the effect on gastric acid secretion of optically pure d-nicotine applied into the lateral cerebral ventricle of anesthetized rats. The interactions of d-nicotine with the I-isomer on gastric acid secretion in rats and on their convulsive actions in mice were also given attention.

Male Wistar rats weighing 220–250 g were anesthetized with urethane (1 g/kg, i.p.) after a 16 hr fast. After wash-out of the stomach with saline, 2 ml of artificial gastric juice prewarmed to 38°C was placed in the stomach at the beginning of each 15-min collection period via a cannula inserted into the stomach. The composition of the artificial gastric juice was a 1:5 (v/v) mixture of glycine and mannitol adjusted to 300 mosM and pH 3.5 by addition of 0.1 N HCl, according to the method of Blair et al. (8). Acid output was determined by titration of gastric samples to pH 7.0 with 0.01 N NaOH. After a period for stabilization of acid output, determinations in 2 consecutive 15-min collections of gastric juice were then made to establish the basal value.

The test substances dissolved in saline in a volume of 25 μl were administered into the lateral cerebral ventricle with a stainless steel micropipette.

Statistical significance of the data was calculated using Student’s t-test for paired comparison in the same group, and Student’s t-test was used for comparisons in different groups. Mice of the ddY strain weighing 20–25 g were used. The test substances dissolved in saline were administered into the tail vein in a volume of 0.1 ml/10 g body weight. Fifty % convulsive doses of both isomers of nicotine were calculated by the method of Litchfield and Wilcoxon (9). Statistical analysis of the data was performed by Fisher’s exact test.

Optically pure d-nicotine was a gift from Dr. Kisaki of Japan Tobacco and Salt Public Corporation.

The basal level of gastric acid output of the urethane anesthetized rats was 4.4±0.4 μEqH+/15 min (n=36).

d-Nicotine, 1000 μg, intraventricularly applied, significantly increased the gastric acid output. Smaller doses of this alkaloid (5, 50, 200 μg) were without effect (Fig. 1).

Five μg of I-nicotine, intraventricularly applied, significantly increased the gastric acid output, as already reported (1). When
50 µg of d-nicotine was administered simultaneously with 5 µg of L-nicotine, the L-nicotine-induced increase in gastric acid output was almost completely abolished (Fig. 2). The increases in gastric acid secretion from the respective basal levels of the L-nicotine alone and L-nicotine plus d-nicotine treated groups at the 60-min collection period were 9.7±2.3 (n=5) and 1.4±1.9 µEq/H+/15 min (n=6), respectively. There was a significant difference between these two values (P<0.05) (Fig. 2).

From these results, it was considered that d-nicotine acted as an antagonist of L-nicotine in the central nervous system. The possible interaction in inducing convulsion between these two isomers was then examined in mice.

Both L- and d-nicotine induced a tonic convulsion. Fifty % convulsive doses of L- and d-nicotine were 0.34 (0.25–0.48) and 5.10 (4.18–6.22) mg/kg, i.v., respectively. L-Nicotine, 0.4 mg/kg, intravenously administered, induced convulsion in 6 out of 10 mice. When the same dose of L-nicotine was administered 5 min after the administration of 2 mg/kg of d-nicotine, convulsion was observed only in 2 out of 10 mice. This value is significantly different from that for the mice treated with L-nicotine alone (P<0.0042).

D-Nicotine blocked the L-nicotine-induced increase in gastric acid secretion when the d-isomer was simultaneously administered with the L-isomer. The appearance of convulsion induced by L-nicotine was also significantly inhibited by pretreatment with d-nicotine. These results are consistent with the evidence reported by Ikushima et al. that d-nicotine inhibited the L-nicotine-induced efflux of 3H-noradrenaline from isolated rabbit pulmonary artery (7). Thus, it is suggested that d-nicotine has an antagonistic action on the L-isomer in the central nervous system as well as in the peripheral nervous system.

It was reported that the effects of the d-isomer of nicotine are qualitatively similar to those of L-nicotine and that the relative potency of the agonistic action of d-nicotine was low compared to that of L-nicotine (3–7). In the present study, 1000 µg of d-nicotine but not 200 µg increased gastric acid secretion as well as 5 µg of L-nicotine. Furthermore, the relative potency of d-nicotine to L-nicotine in inducing tonic convulsion in mice was approximately 15 times less.

From these results, it is considered that the relative potency of the agonistic action of d-nicotine was low as compared to that of L-nicotine in the central nervous system as well as in the peripheral nervous system, and its agonistic potency varied with the preparations.

Acknowledgment: This work was supported by a
Grant from the Japan Tobacco and Salt Public Corporation.

References


