Alpha-2-Adrenoceptor-Mediated Inhibition of Vagally Induced Gastric Acid Secretion with the Anti-Ulcer Agent DQ-2511

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Abstract—Effects of DQ-2511, a new peripherally acting anti-ulcer agent, on vagally induced gastric acid output and mucosal blood flow (MBF) were investigated in urethane-anesthetized rats with gastric fistula. Intravenous infusion of DQ-2511 (2 or 20 mg/kg/hr, for 30 min) reduced the vagally induced gastric acid output and MBF, and these inhibitory effects were abolished by pretreatment with phentolamine. The DQ-2511-induced inhibition of acid output was abolished with yohimbine, but not with prazosin. These observations suggest that DQ-2511 possesses the properties of an adrenergic alpha-2-adrenoceptor agonist. DQ-2511 presumably acts on adrenergic alpha-2-adrenoceptors located on the parasympathetic neurons in the gastric wall, thereby reducing the vagally-induced gastric acid output.

DQ-2511, 3-2-2-(3,4-dimethoxyphenyl)-ethylamino-2-oxoethylamino-N-methyl-benzamide, was found to inhibit acute experimental gastric and duodenal ulcers, in a dose-related manner (1). In the case of gastric acid output, this peripherally acting anti-ulcer agent significantly suppressed the output in pylorus-ligated rats and also the output induced by 2-deoxy-D-glucose, but was without effect on gastric acid output evoked by carbachol, histamine or pentagastrin. Thus, DQ-2511 seems to act on tissues other than the parietal cells.

In the present study, we examined the effects of DQ-2511 on the gastric acid output induced by electrical vagal stimulation in bilaterally vagotomized rats. Male Wistar rats weighing approximately 400 g were deprived of food for 16 hr, but were allowed free access to drinking water. With the rats under urethane anesthesia (1.2 g/kg, i.p.), the trachea and esophagus were exposed and respectively cannulated and ligated through the cervical incision. Bilateral vagus nerves were carefully separated from the carotid arteries and cut at the cervical portion. The peripheral end of the left side vagus nerve was placed on platinum electrodes. The femoral veins and artery were cannulated for infusion of drugs and to measure the systemic blood pressure, respectively. The abdomen was opened by a midline incision and a round-tip polyethylene cannula (3.5 cm in length and 0.4 cm in diameter) was inserted into the stomach via an incision in the duodenum. The cannula was held in place by two ligatures around the duodenum, one at the oral site and the other at the caudal site of the duodenal incision, and the abdominal incision was sutured. After washing the stomach with saline, 2 ml of gastric solution pre-warmed at 38°C was instilled. The solution, replaced at 15-min intervals, consisted of a 1/5 (V/V) mixture of glycine and mannitol adjusted to 300 mOsmol and pH 3.5 by the addition of 0.1 N HCl, according to Blair et al. (2). Thirty minutes after an initial dose of aminopyrine (30 mg/kg, i.v.), the same agent (6.6 mg/kg/hr) was infused through the femoral vein throughout the experiments to maintain a constant blood level. One hour was allowed to elapse before the start of each experiment for stabilization of the aminopyrine concentration in the blood. After stabilization of the basal acid output, the gastric acid output was evoked by continuous electrical
stimulation of the left vagus nerve, the stimulus parameters being square-wave pulses of 0.5 msec duration, at 3 Hz, supramaximal intensity (0.5 mA). These conditions were the same as reported previously (3-6). The gastric acid output was determined by titration with 0.01 N NaOH and expressed as μEq/15 min. The gastric mucosal blood flow (MBF) was measured by the aminopyrine clearance technique developed by Jacobson et al. (7) and expressed as ml/15 min.

In some experiments, phentolamine (5 mg/kg), propranolol (5 mg/kg), yohimbine (5 mg/kg) or prazosin (5 mg/kg) was given i.m. 45 min before the start of vagus nerve stimulation. The doses of the adrenoceptor blocking agents were determined on the basis of the findings in previous studies (3-6).

When the left cervical vagus nerve was continuously stimulated at 3 Hz, the gastric acid output rapidly increased and reached a steady level within 60 min. This steady level of the acid output was maintained for over 45 min. The gastric MBF also rapidly increased and reached a maximum within 60 min, and a relatively constant level was maintained for over 45 min. Thus, 60 min after the beginning of vagal stimulation, DQ-2511 or...
vehicle was intravenously infused for 30 min. The vehicle (20% polyethylene glycol saline, 0.032 ml/min for 30 min) had no effect on acid output and the MBF induced by vagal stimulation (Fig. 1, left). DQ-2511 (2 and 20 mg/kg/hr, for 30 min) reduced the vagally induced gastric acid output and MBF; at the 8th 15-min collection period, the gastric acid output was reduced to 76.9 and 70.0% of the preadministered values, and MBF was reduced to 79.2 and 73.5%, respectively. These were statistically significant (P<0.05) changes from the corresponding values of the vehicle-infused control rats. After cessation of DQ-2511 infusion, gastric acid output and MBF returned to the values obtained before the perfusion. This agent in the doses used in the present experiment (2–20 mg/kg/hr for 30 min) did not affect the systemic blood pressure.

In previous work, we showed that the vagally stimulated acid output and MBF were reduced by both electrical stimulation of the greater splanchnic nerve (sympathoadrenomedullary system) and infusion of catecholamines and that these inhibitory effects were abolished by the pretreatment with phentolamine (3). In the present experiments, pretreatment with phentolamine at the dose of 5 mg/kg, intramuscularly, 30 min before the start of vagal stimulation abolished the inhibitory effects of DQ-2511 on gastric acid output and MBF (Fig. 1, right). Thus, it is apparent that DQ-2511 inhibits the gastric acid output and MBF through alpha-adrenoceptor-mediated mechanisms.

In the next series of experiments, we found that the DQ-2511-induced inhibition of the vagally induced gastric acid output was abolished by 5 mg/kg of yohimbine, but not by prazosin at 5 mg/kg, intramuscularly administered 30 min before the start of vagal stimulation (Fig. 2). Therefore, DQ-2511 apparently suppresses the vagally induced gastric acid output through alpha-2-adrenoceptor-mediated mechanisms. This corresponds with our previous findings (5) that gastric sympathetic inhibition of the vagally stimulated gastric acid output was abolished by yohimbine, but not by prazosin. In addition, clonidine, an alpha-2-adrenoceptor agonist, inhibited the vagally induced gastric acid output, but had no effect on the bezanchoel-induced gastric acid output. The clonidine-induced inhibition of the vagally induced gastric acid output was consistent with the results of Jennewein (8) and Cheng et al. (9). These observations suggest to us that gastric sympathetic nerves influence the parasympathetic nervous system in the gastric wall, through alpha-2-adrenoceptor mediated mechanisms, and vagally stimulated gastric acid output is inhibited. This assumption was given support in the present
study. DQ-2511 has the properties of an alpha-2-adrenoceptor agonist and peripherally acts on the alpha-2-adrenoceptors located on the parasympathetic nerves in the gastric wall, thereby reducing the vagally stimulated gastric acid output.

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References