Effects of the selective I₁ imidazoline receptor agonist, moxonidine, on gastric secretion and gastric mucosal injury in rats

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1 Previous reports of the effects of α_2 -adrenoceptor stimulation on gastric secretion are inconsistent because it was not clear whether the compounds were activating α_2 -adrenoceptors and/or newly described imidazoline receptors. In the present experiments, the effects of moxonidine, an I₁-imidazoline receptor agonist and antihypertensive agent, on gastric secretion and on experimental gastric mucosal injury were examined.

2 Moxonidine (0.01, 0.1 and 1.0 mg kg⁻¹, i.p.) potently inhibited basal (non-stimulated) gastric acid secretion in conscious rats with an ED₅₀ of 0.04 mg kg⁻¹. Two hours following administration of the highest dose of moxonidine (1.0 mg kg⁻¹), gastric acid output was completely suppressed. Moxonidine also significantly increased intragastric pH, at the two highest doses.

3 The α_2 -adrenoceptor agonist, clonidine (0.01, 0.1 and 1.0 mg kg⁻¹, i.p.) decreased basal acid secretion at the lowest dose (37%) and at the highest dose (46%), while the intermediate dose did not affect gastric acid output.

4 In an ethanol-induced model of gastric mucosal injury, moxonidine decreased the length of lesions at the lowest and highest doses (0.01 and 1.0 mg kg⁻¹) as well as the number of the lesions, at the highest dose (1.0 mg kg⁻¹).

5 In pylorus-ligated rats, moxonidine significantly decreased acid secretion (all doses), total secretory volume (1.0 mg kg⁻¹) as well as pepsin output (1.0 mg kg⁻¹).

6 In comparison to clonidine, moxonidine appears to be a more potent anti-secretory and gastric-protective compound. These data indicate a potential role for imidazoline receptor agonists in the management of gastroduodenal diseases associated with hypertension. The relative contribution of the central and peripheral effects of moxonidine to these gastrointestinal actions remains to be determined.

Keywords: Moxonidine; imidazoline receptor; clonidine; gastric acid secretion; pepsin; gastric ulcer; ethanol; pylorus ligation

Introduction

Although not a consistent finding, many studies have indicated an association between hypertension and gastroduodenal ulcer disease. Epidemiological data indicate that hypertension and gastric ulcer disease significantly overlap in man (Mitana *et al.*, 1990). However, laboratory investigations reveal some inconsistencies with the clinical reports. Both Paré & Schimmel (1986) and Shichijo *et al.* (1991) reported that spontaneously hypertensive rats develop less gastric mucosal damage in response to either chemical or stress challenge. Consequently, several groups examined the direct effects of known antihypertensive agents upon gastric secretion and experimental gastric mucosal damage. The non-selective β -adrenoceptor antagonist, propranolol, was generally associated with gastroprotective and anti-secretory effects (Sankary *et al.*, 1986; Bhandare *et al.*, 1990; Ray *et al.*, 1993). Conversely, the α_2 -adrenoceptor agonist, clonidine, has been associated with both gastroprotection as well as with exacerbation of gastric pathology. Kunchandy *et al.* (1985) reported that clonidine decreased gastric lesions in rats, while Del Soldato (1986) indicated that, depending upon the dose of clonidine used, gastric mucosal injury was either lessened or worsened. Recently, Al-Bekairi *et al.* (1993) demonstrated that clonidine exacerbated ethanol-induced gastric mucosal damage, but also decreased gastric acid secretion and enhanced gastric adherent mucus. Because the acid and pepsin-inhibitory effects of clonidine were blocked by

idazoxan in control rats but not in cholinceptor stimulated rats, Tazi-Saad *et al.* (1992) suggested that the effects of clonidine were most likely mediated centrally, rather than locally on secretory cells in the gut.

Recent studies have indicated that many effects previously attributed to α_2 -adrenoceptor stimulation may in fact involve a novel class of receptor, the imidazoline receptor. It is now appreciated that the antihypertensive action of clonidine is primarily mediated by stimulation of central I₁-imidazoline receptors in the nucleus reticularis lateralis rather than by α_2 -adrenoceptors (Tibirica *et al.*, 1991; Ernsberger *et al.*, 1993). Thus, it is not clear whether the previously reported effects of clonidine on gastric secretion were mediated by α_2 -adrenoceptors and/or imidazoline receptors. Due to the inconsistency in the literature regarding the gastrointestinal actions of traditional centrally-acting antihypertensive agents (α_2 -adrenoceptor agonists), we have now tested the effects of moxonidine in two models of gastric secretion and in a model of experimental gastric mucosal injury.

Methods

Gastric acid secretion

Male Sprague-Dawley rats (180 ± 10 g at the start of the study) were implanted with chronic indwelling gastric cannulae as described previously (Paré *et al.*, 1977). After a 14-day recovery period, all cannulae remained firmly attach-

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ed and produced no untoward effects. Secretory testing in sessions of 3 h occurred in the following sequence: vehicle (saline 1.0 ml kg⁻¹), moxonidine 0.01 mg kg⁻¹, 0.1 mg kg⁻¹, 1.0 mg kg⁻¹ i.p. and vehicle again. Each of these sessions was separated by a 96 h period. Within each secretory testing session, a baseline collection was followed by the injection (i.p.) of the vehicle or moxonidine and two subsequent post treatment collections. Thus, each animal served as its own control and all drug treatments were preceded by a 1 h baseline collection period in which no injection occurred. All drug treatments were both preceded and followed by vehicle injections. The volume of secretion was recorded and aliquots of each sample were titrated to pH 7.0 with 0.01 M NaOH in a Mettler DL-21 autotitrator. The results are expressed as $\mu\text{mol h}^{-1}$. For purposes of comparison, other animals were prepared as described above, but given vehicle and clonidine at doses of 0.01, 0.1 and 1.0 mg kg⁻¹ i.p. as described as above.

Ethanol-induced gastric mucosal injury

Rats ($n = 5$ per group) were randomly assigned to treatment conditions. They were deprived of food, but not water, for 24 h prior to being given 1.0 ml of 75% (v/v) ethyl alcohol (Canadian Industrial Alcohols and Chemicals Ltd., Corbyville, Ontario, Canada) p.o. by gavage (Robert *et al.*, 1979). Vehicle or moxonidine at doses of 0.01, 0.1, or 1.0 mg kg⁻¹ was given i.p. 5 min prior to ethanol. Following ethanol and drug treatment, rats were returned to individual cages without food or water for 2 h, after which time they were killed by cervical dislocation. The stomachs were removed, everted, washed and fixed in 10% (v/v) buffered formalin and the number and cumulative length (in millimeters) of gastric glandular mucosal injury determined under a dissecting microscope with an ocular micrometer by a treatment-'blinded' observer.

Pylorus ligation

Rats ($n = 6$ per group) were randomly assigned to treatment conditions. They were deprived of food, but not water, for 24 h, then, immediately before and throughout the experiment, no access to water was allowed. Under ether anesthesia, a midline laparotomy was used to expose the pylorus which was then ligated with 2-0 silk. Care was taken to avoid trauma to the surrounding vasculature. The incision was closed with silk sutures, and vehicle (saline) or moxonidine (0.01, 0.1 or 1.0 mg kg⁻¹, i.p.) administered. Four hours later, all rats were killed by cervical dislocation and the stomachs were removed and the total volume of secretion was recorded. The samples were then centrifuged at 3000 g to remove residual debris and aliquots taken for determination of acid content as described above. The results were expressed as $\mu\text{mol h}^{-1}$. Other aliquots were taken for pepsin determination according to the method of Dupuy & Szabo (1986) and the results expressed as pepsin output (mg h⁻¹). Gastric mucosal injury was assessed as described above.

Drugs

Moxonidine was a gift from Beiersdorf AG, Hamburg, Germany and was dissolved in 0.9% (v/v) saline and injected i.p. in a volume of 1.0 ml kg⁻¹. Clonidine HCl was obtained from Sigma, St. Louis, MO, U.S.A., dissolved in distilled water and injected i.p. in a volume of 1.0 ml kg⁻¹.

Data analysis

All data are expressed as mean $\pm$ s.e.mean. Conscious gastric acid secretion data were analysed by repeated measures ANOVA followed by the least significant difference test for *post-hoc* comparisons. Data from the other experiments were analysed by factorial ANOVA followed by the Tukey HSD

(honestly significant difference) test for *post-hoc* comparisons (Kirk, 1982).

Results

Gastric acid secretion

Moxonidine significantly reduced basal (non-stimulated) gastric acid secretion when given doses of 0.1 (63% inhibition) and 1.0 (65% inhibition) mg kg⁻¹, i.p. (Figure 1; ED₅₀ = 0.04 mg kg⁻¹). The suppression of gastric secretion persisted into the second hour following moxonidine administration and, in the case of the 1.0 mg kg⁻¹ dose, completely suppressed acid output in this second hour (Figure 1). Moxonidine also increased gastric pH ($P < 0.05$) at the two higher antisecretory doses (Table 1).

Clonidine at a dose of 0.01 mg kg⁻¹ inhibited gastric secretion by 37% in the hour immediately following its injection. At the highest dose of clonidine (1.0 mg kg⁻¹), acid output decreased by 46% in both the first and second hours after its administration. The intermediate dose of clonidine (0.10 mg kg⁻¹) did not affect gastric acid secretion (Figure 2).

Ethanol-induced gastric injury

Ethanol-induced gastric mucosal injury was significantly reduced by the lowest (0.01 mg kg⁻¹) and highest (1.0 mg kg⁻¹) doses of moxonidine (Table 2). At the highest dose, moxonidine significantly reduced both the number and the severity of ethanol-induced gastric lesions.

Pylorus ligation

In pylorus-ligated rats, moxonidine significantly reduced acid secretory volume at the highest dose tested (Table 3). Gastric acid output was significantly suppressed by all doses of moxonidine (58%, 66% and 68% inhibition at doses of 0.01, 0.1 and 1.0 mg kg⁻¹, respectively), while pepsin secretion was significantly reduced by the highest dose of moxonidine. Gastric mucosal injury consequent to pylorus ligation determined by the length of the lesions was significantly reduced only by the 0.1 mg kg⁻¹ dose of moxonidine.

Discussion

In light of numerous differences that exist in response to α_2 -adrenoceptor agonists which contain either a phenethylamine or imidazoline type moiety, a novel class of receptor (imidazoline receptors) has been postulated to account for the actions of the latter group of agents (Hamilton, 1992; Michel & Ernsberger, 1992). Early studies had documented that compounds such as idazoxan, rauwolscline and yohimbine were specific antagonists of α_2 -adrenoceptors relative to α_1 -adrenoceptors (Doxey *et al.*, 1984). Subsequent studies, however, demonstrated that [³H]-idazoxan labelled sites were not adrenoceptors and not labelled with specific tritiated α_2 -adrenoceptor antagonists such as rauwolscline and yohimbine (Michel *et al.*, 1989; 1990). These non-adrenoceptor sites have been recently classified into I₁- and I₂-imidazoline receptor subtypes based on their selectivity for [³H]-clonidine and [³H]-idazoxan, respectively (Ernsberger *et al.*, 1992; Reis *et al.*, 1992). Compounds acting as agonists of I₁-imidazoline receptors have been found to be potentially antihypertensive but exhibit less sedation and anti-salivary effects compared to other centrally acting antihypertensive agents, including clonidine (Chrisp & Faulds, 1992). This decreased incidence of side effects of I₁-specific agents, which previously limited the use of these centrally-acting agents, may conceivably result in an increased interest in this class of antihypertensive compound. Thus, description of additional actions of these agents that may have therapeutic benefits will be of interest.

Figure 1 Effects of moxonidine on basal (non-stimulated) gastric acid output (BAO) in conscious rats. Data are presented as mean $\pm$ s.e.mean, ($n = 8$). Injection of vehicle or moxonidine occurred at the beginning of the second hour of collection. Significant difference in BAO in the second (hatched columns) or the third (cross-hatched columns) hour of collection is shown as $*P < 0.05$ compared with the preinjection baseline hour (open columns).

Figure 2 Effects of clonidine on basal (non-stimulated) gastric acid output (BAO) in conscious rats. Data are presented as mean $\pm$ s.e.mean ($n = 8$). Injections of vehicle as clonidine occurred at the beginning of the second hour of collection. Significant difference in BAO in the second (hatched columns) and the third (cross-hatched columns) hour is shown as $*P < 0.05$ compared with pre-injection baseline hour (open columns).

Table 1 Effect of moxonidine on the pH of basal secretion in conscious rats (mean $\pm$ s.e.mean, $n = 8$)

	Moxonidine (mg kg ⁻¹)				
	Vehicle 1	0.01	0.1	1.0	Vehicle 2
Hour 1	2.2 (0.2)	4.0 (0.3)	1.8 (0.1)	1.9 (0.1)	2.3 (0.1)
Hour 2	2.4 (0.3)	5.3 (0.3)	3.9 (0.3)*	5.5 (0.2)*	1.9 (0.1)
Hour 3	2.4 (0.2)	2.6 (0.2)	3.4 (0.2)*	8.0 (0.2)*	1.7 (0.1)

*Significantly different from hour 1 ($P < 0.05$).

Table 2 Effects of moxonidine on ethanol-induced gastric mucosal injury (mean $\pm$ s.e.mean, $n = 5$)

Moxonidine (mg kg ⁻¹)	Number of gastric lesions	Length of gastric lesions (mm)
0 (Saline)	19.2 $\pm$ 2.2	62.6 $\pm$ 5.8
0.01	14.2 $\pm$ 2.8	37.2 $\pm$ 9.3*
0.1	15.8 $\pm$ 2.3	56.2 $\pm$ 13.4
1.0	6.8 $\pm$ 0.9**	16.4 $\pm$ 4.2**

*Significantly different from saline vehicle ($P < 0.05$);

**Significantly different from moxonidine, 0.01 mg kg⁻¹ ($P < 0.05$).

Table 3 Effect of moxonidine on gastric acid output, secretion volume, pepsin output and mucosal injury in pylorus-ligated rats (mean $\pm$ s.e.mean, $n = 6$)

Moxonidine (mg kg ⁻¹)	Acid output (μmol h ⁻¹)	Secretion vol. (ml)	Pepsin output (mg h ⁻¹)	Number of gastric lesions	Length of gastric lesions (mm)
0 (Saline)	33.0 (2.1)	6.4 $\pm$ 0.5	15.6 $\pm$ 1.9	2.3 $\pm$ 1.8	7.5 $\pm$ 2.1
0.01	13.7 (0.8)*	8.3 $\pm$ 0.7	19.3 $\pm$ 2.3	2.2 $\pm$ 0.9	12.0 $\pm$ 4.2
0.1	11.3 (1.1)*	6.6 $\pm$ 1.0	13.3 $\pm$ 2.7*	2.2 $\pm$ 0.7	4.8 $\pm$ 2.3*
1.0	10.5 (1.2)*	5.2 $\pm$ 0.6**	11.5 $\pm$ 2.5**	2.3 $\pm$ 0.9	5.3 $\pm$ 2.6

Pylorus ligation 4 h; moxonidine i.p. at time 0 (immediately after surgery). *Significantly different from vehicle ($P < 0.05$);

**Significantly different from moxonidine, 0.01 mg kg⁻¹ ($P < 0.05$).

A role for imidazoline receptors and for compounds that are active at these sites, in gastrointestinal function and pathology has not been indicated until now. Moxonidine, an I₁-imidazoline receptor agonist, has been found to exhibit a 70 to 600 fold greater selectivity for the I₁-imidazoline receptor relative to the α_2 -adrenoceptor, depending on the tissue studied and the assay conditions (Ernsberger *et al.*, 1992; 1993). In the present study, moxonidine beneficially altered gastric function at doses which were less than those previously shown to be required to decrease blood pressure in spontaneously hypertensive rats (Chrisp & Faulds, 1992; Irzyniec *et al.*, 1992). Gastric acid secretion in conscious rats was inhibited with an ED₅₀ of 0.04 mg kg⁻¹, i.p. Moxonidine also reduced both acid and pepsin secretion in pylorus-ligated rats and reduced ethanol-induced gastric mucosal injury. Interestingly, moxonidine reduced not only aggressive, pro-ulcerogenic factors such as gastric acid and pepsin, but

also appeared to enhance defensive, anti-ulcerogenic mechanisms that have become the target of recent attention in gastrointestinal drug development (Glavin & Hall, 1992). In particular, intragastric pH was significantly elevated by moxonidine, suggesting a possible action on gastric bicarbonate secretion that remains to be investigated.

The present data with moxonidine are in contrast to comparable experiments with clonidine. For example, Al-Bekairi *et al.* (1993) observed that clonidine exacerbated ethanol-induced gastric damage. In these studies, clonidine also decreased gastric acid secretion to a maximum of 63% at a dose of 0.3 mg kg⁻¹. In the present experiments, the lowest and highest doses of clonidine resulted in 37% and 46% inhibition of basal gastric acid secretion, respectively, while the dose of 0.10 mg kg⁻¹ did not influence acid output. In contrast, moxonidine, at doses of 0.1 and 1.0 mg kg⁻¹, initially resulted in 63% and 65% inhibition of basal acid

output, respectively, but in the case of the 1.0 mg kg⁻¹ dose, this inhibition persisted into the subsequent hour of testing during which 100% suppression of gastric secretion was observed. The contrasting gastrointestinal actions of clonidine and moxonidine thus lend further support to the hypothesis that these compounds act at different sites, α_2 -adrenoceptors and imidazoline receptors, respectively. The relative selectivity of these agonists for their respective receptors as reported by others would support this contention. Clonidine displayed a 5 fold selectivity for the α_{2B} -adrenoceptor over the I₁-imidazoline receptor. Conversely, moxonidine displayed up to a 600 fold selectivity for the I₁-imidazoline receptor (Ernsberger *et al.*, 1992).

Similarly, previous reports of α_2 -adrenoceptor-mediated changes on acid secretion with other purported selective agonists must be re-examined. SKF 35886, a purported α_2 -adrenoceptor agonist, was found to decrease secretion and increase absorption of fluid in the rabbit intestine (Fondacaro *et al.*, 1989). However, studies in our laboratory have indicated that SKF 35886 (2,6 dimethyl clonidine) has a 5 fold greater selectivity for the I₁-imidazoline receptor over the

α_2 -adrenoceptor (Smyth *et al.*, unpublished findings). In fact, we have documented a number of differences with regard to the renal actions of clonidine (α_2 -adrenoceptor agonist) and 2,6 dimethyl clonidine (Smyth *et al.*, 1992; Li & Smith, 1993) consistent with these two agonists functioning at two unique receptors.

In summary, the I₁-imidazoline receptor agonist, moxonidine, suppressed basal gastric acid output in both conscious and anaesthetized rats, decreased pepsin output and decreased ethanol-induced gastric lesions. These studies indicate a potential role for I₁-specific imidazoline receptor agonists in the management of gastroduodenal diseases in addition to their blood pressure lowering activity. The relative contribution of the central and peripheral effects of moxonidine to these gastrointestinal actions remains to be determined.

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