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Verapamil and nifedipine effects on gastric acid secretion and ulcer formation in rats

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Abstract—The calcium channel antagonists verapamil and nifedipine were examined for their effects on conscious basal gastric acid output, stress ulcer formation and on ethanol-induced ulcers. Both compounds significantly reduced gastric acid secretion, however verapamil did so in a dose-related manner. Both verapamil and nifedipine significantly attenuated stress gastric ulcer formation. Nifedipine, at a dose of 32·0 mg kg^{-1}, virtually abolished stress ulcers. Verapamil exacerbated, while nifedipine, at 32·0 mg kg^{-1}, attenuated ethanol-induced gastric ulcers. The differential gastrointestinal effects of these calcium channel antagonists support the existence of multiple classes of calcium channels in the gut and suggest an important role for intracellular calcium and hence, its blockade, in gastric pathophysiology.

Histamine is a critical component of gastric function as well as in disease states such as gastroduodenal ulcer. Histamine exerts its effects in the gut through specific receptors (histamine H_2 receptors) and second messenger systems which result in the accumulation of intracellular calcium. Since calcium appears to be an important component of histamine's action, several researchers have begun investigating calcium channel antagonists with respect to their effects in both normal and stress-challenged gut function. Ogle et al (1985) reported that verapamil decreased restraint-induced ulcers whereas the same compound exacerbated ethanol-induced gastric mucosal damage (Koo et al 1986a). Subsequently, Koo et al (1986b) noted that verapamil inhibited gastric acid accumulation in pylorus-ligated rats, but only at low doses. A dose of verapamil which did not influence gastric acid secretion retained its anti-ulcer effect. However, using the rat isolated, perfused stomach, Canfield et al (1985) found that verapamil did not affect gastric secretion. Wait et al (1985) confirmed the anti-stress ulcer effect of verapamil and also noted that this compound decreased plasma gastrin levels in stressed rats. Recently, we replicated the stress ulcer-ameliorating and ethanol ulcer-enhancing effects of verapamil. We now report that verapamil significantly decreases basal, conscious gastric acid secretion in the chronic gastric fistula rat, and that another calcium channel antagonist, nifedipine, exerts significant anti-secretory and anti-ulcer properties.

Methods

Male Sprague-Dawley rats (200 ± 10 g) were used. They were housed in a temperature (22 ± 1 °C) and humidity (65–70%)-controlled room.

Gastric acid secretion. Rats were prepared with chronic indwelling gastric cannulae as described previously (Pare et al 1977). After a 14 day recovery, gastric secretion testing began. The cannula plug was removed and the stomach rinsed with 20 to 30 mL of 0·9% NaCl (saline). The cannula was then left open and the stomach was allowed to drain for 30 min before three 1 h gastric secretion collection periods. The cannula plug was then replaced and a minimum of 96 h elapsed between successive collections from the same animal. The volume of secretion was recorded and centrifuged at 2500 *g* for 10 min and 1·0 mL aliquots of the supernatant titrated to pH 7·0 with 0·01 M NaOH. Acid output was expressed as milliequivalents per 100 g body weight per hour.

Each 3 h collection period was divided into three separate 1 h intervals. The first hour consisted of a pre-injection baseline. At the beginning of the second hour, all collection vials were changed and injections of vehicle, verapamil or nifedipine were given intraperitoneally. At the beginning of the third hour, vials were again changed and the second post-injection collection period of 1 h ensued. Verapamil HCl (Knoll) was dissolved in distilled water and administered i.p. at doses of 2·0, 4·0, 8·0, 16·0 and 32·0 mg kg^{-1}. Nifedipine (Miles Laboratories, Ltd.) was dissolved in DMSO and administered i.p. at doses of 2·0, 4·0, 8·0, 16·0 and 32·0 mg kg^{-1}.

Groups of 6 rats receiving verapamil or nifedipine were tested over seven collection periods (each separated by 96 h) in the following order: (i) vehicle injection only; (ii) 2·0 mg kg^{-1}; (iii) 4·0 mg kg^{-1}; (iv) 8·0 mg kg^{-1}; (v) 16·0 mg kg^{-1}; (vi) 32·0 mg kg^{-1}; and (vii) vehicle injection only. Thus, each animal served as its own control and all drug injections were preceded and followed by a vehicle injection collection period.

Stress ulcer. Rats were deprived of food but not water for 24 h before a single 3 h period of restraint in a cold (4–6 °C) environment as described previously (Glavin 1980; Pare & Glavin 1986). Immediately before immobilization, groups of 6 rats each were given injections of distilled water vehicle, DMSO, verapamil 8·0, 16·0 or 32·0 mg kg^{-1} i.p. or nifedipine 8·0, 16·0 or 32·0 mg kg^{-1} i.p. Following restraint rats were decapitated and the stomach rapidly removed, washed, and preserved in 10% formaldehyde. Ulcers were evaluated under a dissecting microscope with an ocular micrometer by an observer unaware of treatment conditions. The number and cumulative length (in mm) of the ulcers were recorded.

Ethanol ulcer. The method of Robert (1979) was used. Food-deprived rats were injected with vehicle, verapamil, or nifedipine as described above. Fifteen minutes later, they were given a single p.o. administration of 1·0 mL of 100% ethanol by gavage needle. The were returned to their home cages for 2 h without food or water and then killed and examined as described above.

Statistical analysis

All data were analysed by ANOVA followed by Tukey's HSD test where significance was obtained. All data are expressed as mean ± s.e.m.

Results

Effects of verapamil and nifedipine on basal gastric acid secretion. Verapamil produced a significant dose-dependent decrease in basal gastric acid secretion (Table 1). Nifedipine inhibited gastric secretion, but did not do so to the same extent as did verapamil and did not inhibit acid output in a dose-related manner.

Effects of verapamil and nifedipine on stress ulcer formation and on ethanol-induced ulcers. Both verapamil and nifedipine signifi-

Table 1. Effects of verapamil and nifedipine on basal gastric acid secretion.

Treatment (mL or mg kg^{-1})	Acid output pre-injection baseline hour (m equiv/100 g)	Acid output post-injection hour (m equiv/100 g)	% Reduction from baseline
H_2O (i.p.) 1·0	14·1 (2·1)	13·9 (2·2)	—
DMSO (i.p.) 1·0	9·8 (1·8)	10·3 (1·9)	—
Verapamil (i.p.) 2·0	12·3 (2·2)	5·7 (0·9)*	54%
Verapamil (i.p.) 4·0	16·7 (3·1)	7·7 (1·3)*	54%
Verapamil (i.p.) 8·0	13·2 (2·3)	3·9 (0·6)*	70%
Verapamil (i.p.) 16·0	15·5 (2·8)	2·5 (0·4)*	86%
Nifedipine (i.p.) 2·0	6·9 (0·9)	7·2 (1·3)	+2%
Nifedipine (i.p.) 4·0	9·6 (1·9)	4·3 (0·8)*	55%
Nifedipine (i.p.) 8·0	6·8 (1·3)	4·8 (0·9)	29%
Nifedipine (i.p.) 16·0	6·4 (1·3)	4·3 (0·8)	33%

Values are mean ± s.e.m.
* Significantly less than baseline, $P < 0.01$.

cantly reduced stress ulcer formation in a dose-related manner (Table 2). At the highest dose used (32·0 mg kg^{-1}), both compounds virtually abolished stress ulcerogenesis. Verapamil exacerbated ethanol-induced ulcers at doses of 8·0 and 32·0 mg kg^{-1}, while a dose of 16·0 mg kg^{-1} was somewhat protective. Nifedipine worsened ethanol-induced ulcers at a dose of 16·0 mg kg^{-1} but exerted a slight protective effect at a dose of 32·0 mg kg^{-1}.

Table 2. Effects of verapamil and nifedipine on stress-induced ulcer formation and on ethanol-induced ulceration.

Treatment (mL or mg kg^{-1})	No. of ulcers	Cumulative ulcer length (mm)
H_2O (i.p.) 1·0 + stress	18·0 (0·9)	51·0 (4·1)
DMSO (i.p.) 1·0 + stress	18·1 (2·3)	54·5 (3·9)
Verapamil (i.p.) 8·0 + stress	10·0 (2·9)	12·5 (3·3)*
Verapamil (i.p.) 16·0 + stress	4·3 (1·7)	6·5 (1·9)*
Verapamil (i.p.) 32·0 + stress	3·0 (2·0)	2·7 (1·4)*
Nifedipine (i.p.) 8·0 + stress	14·8 (2·2)	15·6 (1·8)*
Nifedipine (i.p.) 16·0 + stress	6·6 (1·8)	4·2 (1·2)*
Nifedipine (i.p.) 32·0 + stress	1·8 (0·9)	1·0 (0·6)*
H_2O (p.o.) 1·0 + ethanol	9·0 (1·1)	44·0 (3·2)
DMSO (p.o) 1·0 + ethanol	9·8 (1·3)	51·8 (2·3)
Verapamil (p.o.) 8·0 + ethanol	16·5 (1·7)	78·8 (14·7)**
Verapamil (p.o.) 16·0 + ethanol	10·5 (2·3)	22·5 (4·3)***
Verapamil (p.o.) 32·0 + ethanol	22·3 (1·7)	100·1 (8·2)**
Nifedipine (p.o.) 8·0 + ethanol	13·3 (0·9)	41·3 (7·6)
Nifedipine (p.o.) 16·0 + ethanol	16·8 (3·5)	64·2 (15·3)
Nifedipine (p.o.) 32·0 + ethanol	13·2 (1·6)	33·0 (7·2)***

Values are mean ± s.e.m.
* Significantly less than respective vehicle groups; $P < 0.01$.
** Significantly greater than vehicle; $P < 0.01$.
*** Significantly less than vehicle; $P < 0.01$.

Discussion

The present data indicate a significant anti-secretory effect of verapamil and, to a lesser extent, of nifedipine. This effect of verapamil is in contrast to the findings of Koo et al (1986b) who showed that a small (2·0 mg kg^{-1}) dose of verapamil did not affect acid accumulation in pylorus-ligated rats, while a dose of 4·0 mg kg^{-1} significantly reduced acid output in this model. The observed differences in the apparent potency of verapamil and nifedipine in attenuating gastric acid secretion may be due to inherent differences between the pyloric occlusion model and the chronic gastric fistula model used in the present studies. Nevertheless, it appears that calcium channel antagonists have a role in modulating gastric acid secretion. In fact, one report (Caldara et al 1985) suggested a potentially clinically useful effect of nifedipine in attenuating gastric secretion in man. Whether such an effect is a direct action of calcium channel antagonism or an indirect effect, perhaps through effects on mucosal blood flow (Sewing 1984; Bouclier & Spedding 1985) remains to be determined.

Both verapamil and nifedipine markedly reduced restraint stress ulcer formation. At the highest dose employed in this study (32·0 mg kg^{-1}), nifedipine virtually abolished stress ulcer development. The findings with verapamil are consistent with those of Koo et al (1986b) and extend the anti-stress ulcer properties of verapamil over a wider dose range. It is interesting that nifedipine was less potent than verapamil in obtunding gastric acid secretion, but was more effective than verapamil in attenuating stress ulcer formation. Consistent with the interpretation of Koo et al (1986b), these findings indicate that the anti-secretory action of nifedipine may not account for its anti-ulcer effects. Studies are underway to characterize further the mechanism(s) underlying the anti-ulcerogenic effects of nifedipine.

Verapamil worsened ethanol-induced ulcers, while nifedipine, only at a dose of 32·0 mg kg^{-1}, attenuated these gastric lesions. While the verapamil data are consistent with previous reports (Koo et al 1986a), the nifedipine data are novel and suggest a different mechanism of action for these two calcium channel antagonists, possibly through actions at different types of calcium channels (Spedding 1987).

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