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Effects of Catecholamine Agonist and Antagonist Drugs on Acute Stomach Ulceration Induced by Medial Hypothalamic Lesions in Rats[1]

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NOBREGA, J. N. AND N. I. WIENER. *Effects of catecholamine agonist and antagonist drugs on acute stomach ulceration induced by medial hypothalamic lesions in rats.* PHARMACOL BIOCHEM BEHAV **19**(5) 831–838, 1983.—In order to investigate the involvement of catecholamines (CAs) in acute stomach ulceration induced by hypothalamic lesions, rats were given bilateral electrolytic anodal lesions in the medial hypothalamus followed by a single subcutaneous injection of CA agonist or antagonist drugs. As in previous studies, lesioned rats that received no post operative drug treatment showed extensive gastric damage when examined 24 hr after the brain lesion. Chlorpromazine, amphetamine, desipramine and isoproterenol caused significant reductions in the extent (total length) and/or number of erosions induced by the brain lesion. Haloperidol and propranolol did not seem to affect ulcer formation. Clozapine increased the number but not the total length of ulcers. Phentolamine, alone or in combination with propranolol, significantly increased both the number and total length of lesion-induced ulcers. Similarities between these results and those reported for most of these drugs in the context of ulcers induced by various experimental stress procedures suggest a degree of commonality between acute stress ulcers and ulcers induced by hypothalamic lesions. The overall pattern of results obtained is also consistent with evidence indicating a protective role for catecholamines in acute ulcer formation.

Catecholamines Hypothalamic lesions Gastric ulcers

THE central nervous system (CNS) is widely acknowledged to play an important role in the etiology of ulcerative gastrointestinal disorders, including the so called "acute stress ulcers" that may occur following surgical or physical trauma, burns, sepsis or head injury [23,33]. Accordingly, a number of experimental "stress" procedures for the induction of gastric erosions in laboratory animals have been developed. These include physical restraint, exposure to cold, water immersion, shock schedules and motor overexertion (cf., [31]). Such experimental stress procedures may arguably provide better models of acute ulcer formation than do manipulations that bypass the CNS altogether and affect the gastrointestinal tract directly, such as pylorus ligation or local infusion of steroids, histamine releasers, acids, or other compounds. Yet, being essentially environmental manipulations, stress procedures do not necessarily provide any clue as to relevant CNS mechanisms involved in ulcerogenesis.

An alternative, but as yet relatively unexplored approach to the experimental modeling of acute ulcer formation is provided by direct manipulations of the CNS by means of brain stimulation or lesion procedures [15,17]. It has been known since the last century that tumors or lesions in certain brain areas can be associated with severe gastric damage in humans [1,7]. Experimental lesions of the hypothalamus or other limbic structures have been shown to induce gastric ulceration in a variety of species, including rats, guinea pigs, cats, dogs and monkeys. In rats, we have recently shown that gastric lesions can develop as early as 3 to 4 hours after electrolytic anodal lesions in the medial or lateral hypothalamus and are reliably observed in more than 80% of the animals 24 hr after the brain lesion [27]. Of particular interest is the apparent similarity between the gastric erosions induced by hypothalamic lesions and those typically observed after stress procedures in animals. Thus, both hypothalamic

[1]Some of the data reported here were included in a Ph.D. dissertation submitted to York University by the first author in 1980. A partial report of these results was presented at the 10th Annual Meeting of the Society for Neuroscience, Cincinnati, OH, 1980.

lesion- and stress-induced ulcers are usually confined to the glandular, acid-bearing part of the stomach (local manipulations such as pylorus ligation can induce ulcers in the nonglandular part of the stomach); both types of ulcers are usually superficial erosions of the mucosa, not necessarily penetrating the muscularis proper, as in the case of the acute stress ulcer in humans; both are reduced by the presence of food or non-nutritive bulk in the stomach [29]; and both are blocked by anticholinergic drugs or subdiaphragmatic vagotomy [13, 14, 19]. Yet, it must be noted that ulcers induced by hypothalamic lesions are not merely the result of nonspecific surgical stress, for not all brain lesion placements induce stomach ulceration [27].

The precise mechanisms of ulcerogenesis remain to be determined both in the case of stress- and brain lesion-induced ulcers. The fact that vagotomy and anticholinergic drugs are effective in blocking hypothalamic- and stress-induced ulcers indicates the importance of an active parasympathetic component in both cases. The role of the sympathetic nervous system is less clear. The effects of drugs affecting catecholamines and the sympathetic nervous system have been studied in several ulcer-inducing models, but not, to our knowledge, in connection with hypothalamic-induced gastric ulceration. Therefore, the aim of the present study was to to explore further similarities between brain lesion- and stress-induced ulceration by investigating the effects of several drugs affecting catecholamine systems on gastric ulceration induced by hypothalamic lesions.

METHOD

Subjects

Male Wistar rats (High Oak Ranch and Woodlyn Farms, Guelph, ON) with weights ranging from 300 to 450 g were used. The animals were kept in groups of 4 or 5 with food and water ad lib until the time of surgery. Temperature was kept at 21±1 °C. Lights in the vivarium were on from 0700 to 1900 daily.

Surgery

Lesioning electrodes consisted of No. 00 stainless steel insect pins insulated with 3 coats of Epoxylite except for 0.3 to 0.5 mm at the tip. Under sodium pentobarbital anesthesia (60 mg/kg body weight, IP), bilateral lesions were produced by passing 1 mA anodal current for 30 sec through electrodes aimed at the following stereotaxic coordinates: 0.2 mm anterior to bregma, 0.7 mm lateral to the sagittal suture, and 9.0 mm ventral to the skull surface, with the incisor bar set 5.0 mm above the interaural plane. These coordinates and lesion parameters have been shown to result in a high incidence of stomach ulcers [27]. No supplementary anesthesia, atropine or antibiotics were used before or after surgery. Control animals were anesthetized, placed in the stereotaxic frame, and had holes drilled in the skull, but electrodes were not lowered into the brain.

Post-Operative Procedure

Immediately after surgery animals were placed in individual cages. No food or water was available to the animals during the 24 hr survival period, for intoxication and death often result from voracious eating and drinking in the hours immediately following such lesions [43]. In addition, presence of food in the stomach can reduce ulceration after hypothalamic lesions [29].

Drug Injections

Catecholamine antagonists tested included the dopamine (DA) and noradrenaline (NE) receptor blocker chlorpromazine (Sigma), the DA receptor blockers haloperidol (McNeil) and clozapine (Sandoz), the alpha adrenergic blocker phentolamine (Mount Royal), and the beta adrenergic blocker propranolol (Ayerst). Among the catecholamine agonists tested, D-amphetamine (Smith Kline and French) and the monoamine oxidase inhibitor pargyline (Sigma) are known to increase the synaptic availability of NE; desipramine (Ciba Geigy) increases the synaptic availability of NE, and isoproterenol (Sigma) is a beta adrenergic receptor stimulant. The main criterion for dose selection was previous inclusion of the same doses in studies using other experimental ulcer models.

One and a half hours after the brain lesion or sham surgery, each animal received one subcutaneous injection of freshly prepared drug solution or vehicle. The only exception was pargyline, which was given 4 hr before the brain lesion. Timing and route of injection were intended to ensure that maximal drug levels occurred within the first 3 to 4 hr after the brain lesion, when most of the erosions seem to develop [27]. Injection time was also chosen to coincide with the time when most animals were regaining righting reflexes and becoming ambulatory again after anesthesia. A minimum of 6 rats were initially prepared in each drug dose group. All drugs were dissolved in 0.85% saline, except for haloperidol and clozapine, which were dissolved in 1% acetic acid. Drug doses were calculated as free base.

Histological Examinations

Twenty-four hr after the brain lesions all animals were anesthetized with chloroform. Stomachs were removed, cut along the greater curvature, examined for the presence of hemorrhage, and washed once in tap water or saline. Rugal folds in the mucosa were then carefully smoothed out so that erosions could be examined and measured. An "ulcer" was defined as any break or discontinuity in the gastric mucosa. Total ulcer length was the main index of stomach damage used. It was defined as the summation of the length plus largest width of each erosion [30] as measured under 7-fold magnification. A second measure, number of ulcers, was also recorded, even though it may not be a very sensitive index, since small ulcers may fuse into bigger ones along rugal folds. However, since number of ulcers has been widely used in ulcer research, it was included in the present study for comparative purposes. The occurrence of other abnormalities such as hemorrhages, softening of the stomach wall, ischemia and inflammation was also noted.

After perfusion through the heart with 0.9% saline and 10% formalin, brains were removed and stored in 10% formalin for at least 7 days. Fifty-micron sections were cut through the lesion area, mounted on microscope slides, and placed on a photographic enlarger to produce prints of unstained sections. Data from animals with lesions entirely outside of the medial hypothalamus were discarded.

Statistical Analyses

The total length of ulcers per stomach was analyzed by computer-aided analyses of variance, and single group com-

TABLE 1

EFFECTS OF CATECHOLAMINE ANTAGONISTS ON STOMACH ULCERATION INDUCED BY HYPOTHALAMIC LESIONS

Drug Group	Dose (mg/kg)	N	Ulcers Number§	Ulcers Incidence (%)
Non-lesioned Controls		12	0‡	2/12 (17)‡
Lesion + Vehicle		14	2.0	13/14 (93)
Chlorpromazine	3	6	1.0	5/6 (83)
	10	8	1.0	6/8 (75)
	30	10	0‡	2/10 (20)‡
Haloperidol	1.5	10	1.5	9/10 (90)
	4.5	6	2.0	6/6 (100)
	9	5	4.0	5/5 (100)
Clozapine	3	4	10.0‡	4/4 (100)
	12	5	4.5*	5/5 (100)
	18	7	8.0‡	7/7 (100)
Phentolamine	3	5	4.0*	5/5 (100)
	12	5	8.5‡	5/5 (100)
	36	6	9.0†	6/6 (100)
Propranolol	3	6	7.5†	6/6 (100)
	12	6	2.0	5/6 (83)
	36	5	3.0	4/5 (80)
Phentolamine	12			
+ Propranolol	12	8	25.0	8/8 (100)

§Values are Medians.

*$p<0.05$; †$p<0.01$; ‡$p<0.001$. Mann-Whitney test (number) or z test for proportions (%), compared to lesion + vehicle group.

parisons were done by means of orthogonal or non-orthogonal ANOVA contrasts. Since number of ulcers per stomach was found to follow a highly skewed distribution, the non-parametric Mann-Whitney test was used to analyze differences between groups on this variable.

RESULTS

Immediately upon recovery from anesthesia, lesioned animals began to show signs of motor hyperactivity, which rapidly intensified and reached a peak at four to five hours after the lesion, as previously described [27,43].

Twenty-four hours after the lesions gastric pathology was observed in 13 of 14 rats that had received hypothalamic lesions followed by vehicle injections. Two small erosions were found in one of the 12 non-lesioned controls (Table 1). In the lesioned group, ulcers consisted mostly of round or elongated mucosal erosions in the glandular stomach, with a hemorrhagic base and borders. A common occurrence was the presence of two symmetric tear-drop shaped hemorrhagic ulcers on each half of the stomach, with smaller, round, non-hemorrhagic erosions scattered about. Free hemorrhage and ischemia were not frequently seen, but most erosions appeared to be surrounded by areas of inflammation.

Histological Results

Histological findings were similar to those described in detail in our previous work [27]. Virtually all brain lesions were confined to a medial hypothalamic zone bounded laterally by the fornices. On the anterior-posterior plane lesions extended from 0.6 anterior to 0.8 mm posterior to bregma, with the greatest diameter of most lesions (approximately 1.5 mm) at the rostral third of the ventromedial nucleus. In addition to the ventromedial nucleus, lesions often involved parts of the anterior hypothalamic area, the dorsomedial, and/or the paraventricular hypothalamus. Ventral thalamic structures were generally not affected. Figure 1 shows a representative ulcer-inducing hypothalamic lesion placement. In the lesion + vehicle group no correlations were apparent between lesion size or placement within the hypothalamus and severity or type of stomach pathology.

Effects of Catecholamine Antagonists

Figures 2, 3 and 4 show drug effects on total ulcer length, with mean values for each drug group expressed as a percentage of the mean for the lesion + vehicle group. Tables 1 and 2 show data on number and incidence of ulcers in each group.

Chlorpromazine reduced the gastric ulceration induced by hypothalamic lesions in a non-linear fashion (Table 1 Fig. 2). The higher dose (30 mg/kg) was the most effective in this respect, followed by the lowest dose (3 mg/kg). In the 30 mg/kg group, erosions were completely absent in 8 of 10 rats, but mucosal inflammation, free hemorrhage, loss of tonus and ischemia were present in 5 of those animals. Analyses of the drug main effect indicated that across the dose range

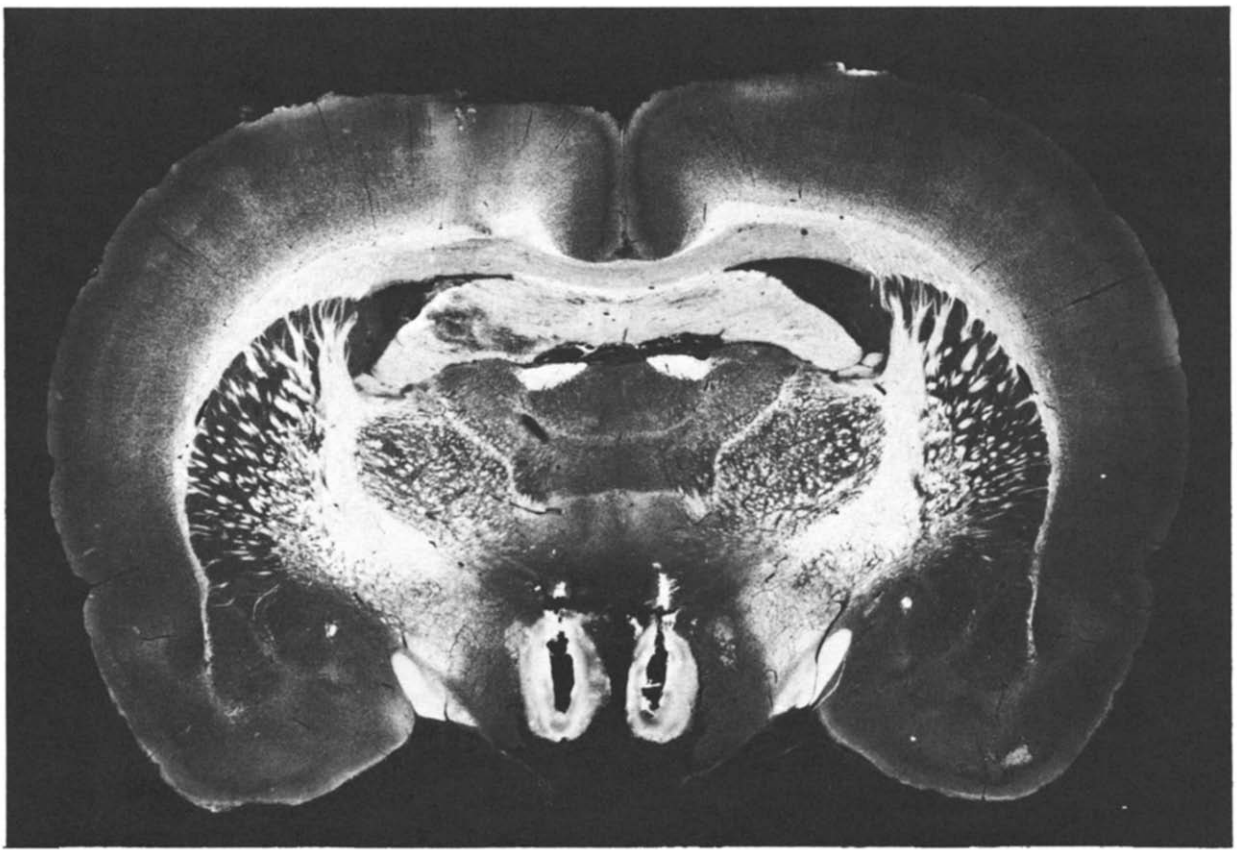

FIG. 1. Photomicrograph of unstained brain section showing typical ulcer-inducing lesion placement in the medial hypothalamus.

tested chlorpromazine significantly reduced both the total length ($p<0.02$) and the number of erosions ($p<0.03$).

Haloperidol did not significantly affect ulcer formation, although a trend was apparent for higher doses to result in increased ulceration. In addition to erosions, mucosal discoloration and localized inflammation were seen in 3 of 16 rats. Clozapine significantly aggravated lesion-induced ulceration in terms of number of ulcers across all doses ($p<0.01$), but not in terms of total ulcer extent. This was due to the fact that erosions in the three clozapine groups were usually quite small, less than 1 mm in length.

Phentolamine significantly increased both the number ($p<0.001$) and total lengh ($p<0.03$) of lesion-induced ulcers (Table 1 and Fig. 3). In the 36 mg/kg group 4 animals died within 6 hr of the lesion (data not included in the analysis). One of the surviving rats in this group had ulcers in the antrum, a compartment of the rat stomach containing only mucus-secreting cells, where ulcers are not usually found. All rats receiving phentolamine had ulcers, but other types of gastric pathology were generally absent.

The lowest dose of propranolol (3 mg/kg) significantly increased the number of ulcers, but the other two doses appeared to have effects in the opposite direction. Across the three dose levels propranolol had no significant effect on either number or extent of lesion-induced ulcers. Three out of 17 rats showed no gastric abnormalities. Discoloration and localized patches of inflammation occurred in two stomachs in the 36 mg/kg group. Another stomach in this group showed fluid accumulation and loss of tonus.

When phentolamine and propranolol were combined in a single injection (12 mg/kg of each drug) a drastic increase was observed in both the number ($p<0.001$) and length ($p<0.001$) of lesion-induced ulcers. The mean number of ulcers per stomach increased by nearly 600% and the total ulcer length by more than 300% over the lesion + vehicle means (Fig. 3). A separate group of rats was then given the phentolamine plus propranolol injection in the absence of hypothalamic lesions. Localized reddening of mucosa was seen in 5 out of 6 of these rats, but no erosions were observed.

Effects of Catecholamine Agonists

As shown in Fig. 4 and Table 2, each of the four drugs used to potentiate catecholamine activity reduced lesion-induced gastric ulceration to some extent. There were, however, important differences in the appearance of stomachs in the various drug groups.

Total ulcer length was reduced in amphetamine-treated rats ($p<0.004$), but other signs of pathology were frequent in both dose groups. Free hemorrhage was seen in 2 of 5 stomachs in the 2 mg/kg group and submucosal hemorrhage in three others. Fluid and gas accumulation, causing dilation of the stomach, occurred in 2 of 6 rats in the 6 mg/kg group. The latter stomachs also showed loss of tonus and softening of the gastric wall. The stomachs had a flaccid consistency, instead of the usual contracted appearance.

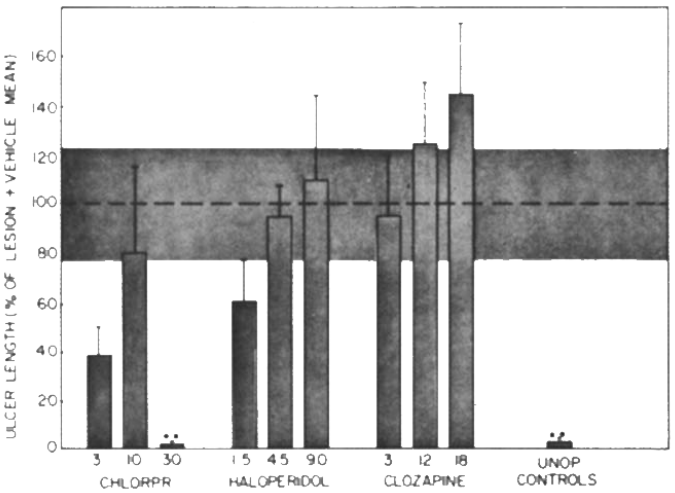

FIG. 2. Effects of catecholamine antagonists on lesion-induced ulceration. Values are expressed as percent of lesion + vehicle group. shaded area represents S.E. of lesion + vehicle mean. *$p<0.05$; **$p<0.01$; ***$p<0.001$. ANOVA comparisons with lesion + vehicle group. Numbers under bars indicate drug dose in mg/kg body weight. Chlorpr.: chlorpromazine; Unop. controls: unoperated controls. Group sizes are given in Tables 1 and 2.

Isoproterenol had a significant protective effect against lesion-induced ulcers both in terms of number ($p<0.01$) and length ($p<0.001$). No signs of gastric pathology of any sort were seen in 3 out of 20 rats. One stomach showed fluid accumulation and loss of tonus, one had ischemic patches and free hemorrhage, and another had signs of submucosal bleeding.

Desipramine also provided significant protection against lesion-induced ulceration (number: $p<0.01$; length: $p<0.01$). Nine out of 12 stomachs in the two desipramine groups showed no signs of pathology.

Finally, the total ulcer extent in pargyline-treated rats was approximately 60% less than in lesion + vehicle controls ($p<0.05$), although no changes in number of ulcers were apparent. Loss of tonus and fluid accumulation were seen in one stomach, which was otherwise free of erosions. Discoloration, inflammation and free hemmorrhage were not observed in this group.

DISCUSSION

The general pattern of chlorpromazine effects on lesion-induced ulceration in the present study—including the overall attenuation of pathology, the virtual blockade at the highest dose, and the apparent lack of linear dose-response relations [4,38]—is quite consistent with the reported effects of this drug on other types of experimentally-induced ulcers. Chlorpromazine has been reported to reduce ulceration and/or hemorrhage induced by electric shock schedules [38]; electric shock plus exposure to cold [36]; pylorus ligation [11]; restraint [4,16]; restraint plus cold [6,9]; water immersion [25,39] and forced activity [35].

Chlorpromazine has considererable gastric antisecretory activity [2], which may be important to its ulcer-reducing properties. There is also evidence that these effects of chlorpromazine are centrally mediated and not due to peripheral anticholinergic activity. Brodie *et al.* [5] found that chlorpromazine was effective in inhibiting gastric secretion when injected directly into the cerebral ventricles. Yamaguci *et al.*

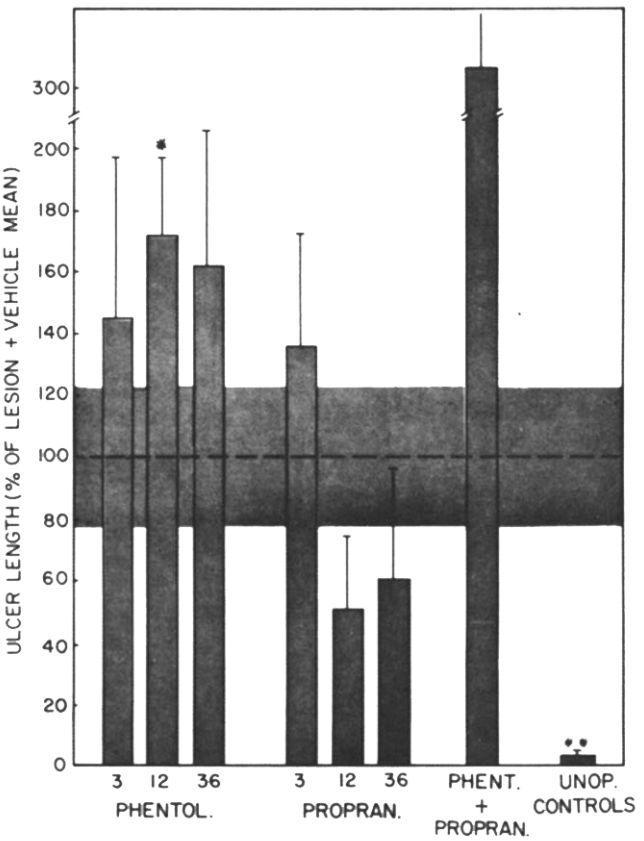

FIG. 3. Effects of catecholamine antagonists on lesion-induced ulceration. See caption for Fig. 2. Phentol.: phentolamine; Propran.: propranolol.

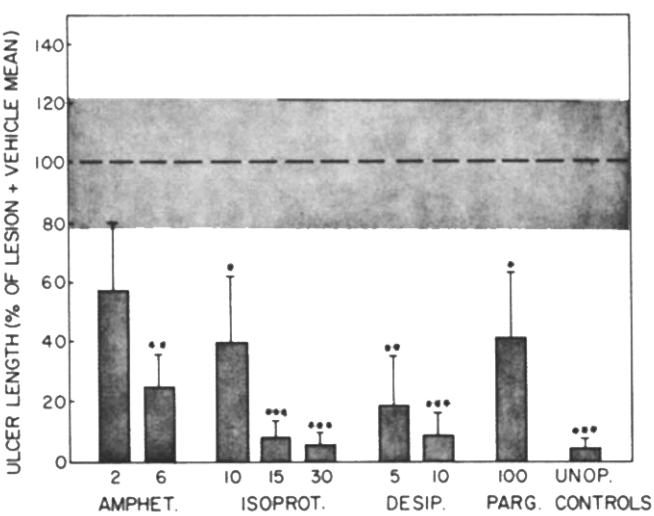

FIG. 4. Effects of catecholamine agonists on lesion-induced ulceration. See caption for Fig. 2. Amphet.: amphetamine; Isoprot.: isoproterenol; Desip.: desipramine; Parg.: pargyline.

TABLE 2

EFFECTS OF CATECHOLAMINE ANTAGONISTS ON STOMACH ULCERATION INDUCED BY HYPOTHALAMIC LESIONS

Drug Group	Dose (mg/kg)	N	Ulcers	
			Number§	Incidence (%)
Non-lesioned Controls		12	0‡	2/12 (17)‡
Lesion + Vehicle		14	2.0	13/14 (93)
Amphetamine	2	5	3.0	4/5 (80)
	6	6	2.5	4/6 (67)
Isoproterenol	10	6	1.0*	3/6 (50)‡
	15	5	0*	1/5 (20)‡
	30	9	0*	2/9 (22)‡
Desipramine	5	6	0†	2/6 (33)‡
	10	6	0†	1/6 (17)‡
Pargyline	100	4	2.0	3/4 (75)

§Values are Medians.

*$p<0.05$; †$p<0.01$; ‡$p<0.001$. Mann-Whitney test (number) or z test for proportions (%), compared to lesion + vehicle group.

[44] found that the antisecretory effects of chlorpromazine were abolished in rats depleted of catecholamines by reserpine pretreatment, suggesting that the effect was not due to direct anticholinergic action.

In contrast to chlorpromazine, the dopamine (DA) receptor antagonists haloperidol and clozapine provided no protection against lesion-induced ulcers. Indeed, clozapine significantly increased the number of ulcers. This would suggest that the protective effects of chlorpromazine are probably not due to its DA receptor blocking activity.

The beta-adrenergic blocker propranolol produced mixed results, the lowest dose tending to aggravate ulceration, while the two higher doses appeared to reduce it. Published results with this drug on other ulcer models have also been inconsistent. Rosoff and Goldman [37] reported an increase in the number and severity of restraint-induced ulcers, whereas Okabe *et al.* [28] found a decrease in ulceration induced by water immersion stress in propranolol-treated rats. In yet other studies propranolol was reported to have no effect on stress-induced ulcers [8,39].

Lesion-induced ulcers were aggravated by alpha adrenergic blockade with phentolamine. This has also been reported to occur in the case of ulcers induced by water immersion [28] and restraint stress [8]. Restraint ulcers can also be exacerbated by another alpha-adrenergic blocker, phenoxybenzamine [37]. Worsening of human ulcers after phentolamine has also been documented [26]. However, Djahanguiri *et al.* [10] reported a decrease in restraint ulcers after phenoxybenzamine or phentolamine.

Simultaneous blockade of both alpha and beta adrenergic receptors by phentolamine plus propranolol resulted in a pronounced aggravation of lesion-induced ulceration. It is noteworthy in this respect that both phentolamine and propranolol are reported to have antisecretory effects on the rat stomach [2, 8, 28, 39]. On the other hand, phentolamine does have effects on gastric circulation [9] and motility [26], which may be relevant to the aggravation of gastric ulcers by this drug.

The fact that all the catecholamine agonists tested in the present study reduced stomach ulceration by 60% or more suggests a significant protective role for catecholamines in lesion-induced gastric ulceration. As to comparisons with other types of experimental ulcers, not much work has been done with the particular CA agonists used in the present study, with the exception of desipramine and related tricyclic antidepressant drugs. Thus, imipramine, desipramine and amitriptyline have been shown to reduce ulcers induced by a number of different stress procedures (e.g., [3, 4, 5, 21, 30]). One of the best known effects of desipramine is to prevent reuptake of noradrenaline into presynaptic terminals. Other drugs not in the tricyclic group which also block noradrenaline reuptake have been shown to be equally effective against stress-induced ulceration [21,22]. Desipramine does have gastric antisecretory effects. As in the case of chlorpromazine, there is evidence that such effects are centrally mediated. Recent work by Pendleton *et al.* [32] indicates that central noradrenergic neurons are involved in the antisecretory effects of desipramine.

Considered as a whole, the results of the various drug manipulations in the present study clearly indicate a permissive role for catecholamines in acute ulcer formation after hypothalamic lesions. Moreover, the evidence seems to be stronger for an involvement of noradrenergic (or adrenergic) mechanisms than for dopaminergic mechanisms. However, the data obtained with chlorpromazine, haloperidol and clozapine indicate the need to further investigate the specific role of dopaminergic systems in acute ulcerogenesis.

The exact mechanism whereby hypothalamic lesions induce acute gastric pathology remains unknown. The use of systemic drug injections may be of interest in terms of potential therapeutic implications. On the other hand, this approach allows no more than speculations concerning the issue of the respective involvement of central vs. peripheral catecholamine systems in the drug effects observed here. For example, medial hypothalamic lesions similar to the ones in the present study have been shown to cause acute increases in gastric acid secretion [34]. It is thus possible to speculate that some of the drugs that potentiate noradrener-

gic transmission may have produced their ulcer-inhibiting effects by enhancing sympathetic activity to match lesion-induced increased vagal-parasympathetic activity. They might also be acting on central noradrenergic systems, perhaps partially rectifying the acute effects of hypothalamic lesions on those systems. Consistent with the possibility of a critical involvement of central catecholaminergic sites are preliminary results from our laboratory indicating that drugs such as chlorpromazine and desipramine are also effective against lesion-induced ulceration when injected directly into the ventricular system.

Irrespective of whether the drug effects observed here are primarily related to central or to peripheral systems, one of the major findings of this study is that lesion-induced ulcers respond to various pharmacological agents virtually in the same way as ulcers caused by environmental stress procedures. This may be of interest in view of growing evidence that limbic forebrain structures are involved in ulcers induced by stress procedures (e.g., [12, 18, 20]) and even in ulcers induced by substances such as cinchophen and nicotine, which were previously thought to act directly on the stomach wall [24,40].

The above observations suggest a degree of commonality between mechanisms involved in ulcer formation induced by different types of experimental manipulations. In this context, the potentially most important aspect of the brain lesion model of ulcer formation is that it may allow more direct investigation of actual structures, systems and mechanisms involved in neurogenic gastric pathology. While stress procedures manipulate environmental factors and local treatments act directly on the target organ, CNS manipulations offer the possibility of tapping those systems that may constitue the crucial link between the environment and the target organ in ulcerogenesis.

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