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The Effects of Buspirone, a Selective Anxiolytic, on Stress Ulcer Formation in Rats[1]

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SULLIVAN, R. M., P. G. HENKE AND A. RAY. *The effects of buspirone, a selective anxiolytic, on stress ulcer formation in rats.* PHARMACOL BIOCHEM BEHAV 31(2) 317–319, 1988.—The effects of buspirone hydrochloride were investigated on the formation of cold-immobilization gastric stress ulcers. Low doses significantly attenuated, while higher doses greatly potentiated gastric stress pathology. The dopamine antagonist haloperidol, and the agonist apomorphine respectively, reversed the buspirone effects. The role of dopamine in the expression of buspirone's effects is discussed, although other transmitter systems may mediate some of the actions of buspirone.

Buspirone Stress ulcer Dopamine Anxiety Nonbenzodiazepine

MUCH interest has recently been focused on the mechanisms of action of buspirone, a nonbenzodiazepine compound, with selective anxiolytic properties (2, 16–18). The lack of such side effects as cognitive impairments and physical sedation (11,12), along with its inability to serve as a positive reinforcer (16), have suggested the great clinical potential of buspirone, in the treatment of anxiety. Initial studies of buspirone action revealed pronounced effects on brain dopamine (DA) systems (13, 16), with little or no effect on other transmitter systems. Buspirone was proposed to possess properties, similar to both DA agonists and antagonists depending on dosage levels (16,18).

Reduced reactions to stress following antianxiety agents, have been reported in several animal studies (1, 4, 6, 7,). The role of central DA systems during stressful situations has recently come to light. Enhanced DA activity has been observed in response to stress (8,19), and stress ulcers (induced by cold-immobilization), have been consistently attenuated by DA agonists, administered both peripherally and centrally, whereas DA antagonists tended to facilitate stress ulcer formation (5, 9, 14, 15). In fact, DA antagonists have been shown to induce ulcers in nonstressed rats (15). We, therefore, sought to determine the effects of low and high doses of buspirone on stress-induced gastric pathology, and its possible relation to DA systems.

METHOD

Male Wistar rats, 90–120 days old (Charles River, Quebec), were used in the study. They were housed individually in light and temperature controlled rooms, with free access to food and water. Rats were food-deprived 24 hr prior to drug or vehicle injections (IP), followed immediately by immobilization in Plexiglas restrainers (Fisher Scientific). Following 3 hr of cold-immobilization (4°C), rats were sacrificed with an overdose (IP) of sodium pentobarbital (Somnotol, MTC Pharmaceuticals, Mississauga). While deeply anesthetized, stomachs were removed, cut along the greater curvature, washed in cold water and examined microscopically (×10) for mucosal lesions. The number of lesions and their severity (cumulative length to the nearest 0.1 mm) were recorded.

Drugs used in the study included buspirone hydrochloride (Bristol-Myers), haloperidol and apomorphine hydrochloride (both from Sigma). Buspirone was dissolved in distilled water. Haloperidol and apomorphine were dissolved in a few drops of acetic acid, pH adjusted to 5.5 with NaOH and the volume made up with distilled water. Control rats were either injected with this vehicle or distilled water alone. All injections were made in a volume of 1 ml/kg. In rats receiving two injections, initial injections always preceded the second by 40 min.

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TABLE 1
MEAN GASTRIC PATHOLOGY FOLLOWING BUSPIRONE AND DOPAMINERGIC AGENTS

Treatment (mg/kg, IP)	n	Gastric Pathology (Mean ± S.E.M.) Ulcer Number	Severity (mm)
Controls	6	6.2 ± 0.48	1.7 ± 0.22
Buspirone (0.3)	6	2.2 ± 0.88†	1.7 ± 1.04
Buspirone (1.0)	6	2.2 ± 0.58†	0.8 ± 0.32*
Buspirone (3.0)	6	8.8 ± 1.40	4.6 ± 1.02
Buspirone (10.0)	6	19.0 ± 4.35*	11.5 ± 3.07‡
Buspirone (30.0)	5	33.8 ± 3.38†	32.2 ± 9.39†
Haloperidol (1.0)	6	9.0 ± 1.16*	2.8 ± 0.70
Apomorphine (5.0)	6	1.7 ± 0.22‡	0.4 ± 0.10‡
Hal (1) + Busp (1)	6	5.5 ± 0.57¶	5.3 ± 2.77§
Busp (10) + Apo (5)	6	14.0 ± 3.12	11.7 ± 3.32†
Apo (5) + Busp (10)	6	9.2 ± 2.60	6.5 ± 2.70

*$p<0.05$; †$p<0.01$; ‡$p<0.002$ (compared to controls); §$p<0.05$; ¶$p<0.01$ [compared to Buspirone (1.0)].
All comparisons by Mann-Whitney U-test (two-tailed).

The results were analyzed using the Kruskal-Wallis one-way ANOVA for nonparametric data, followed by Mann-Whitney U-tests (two-tailed) for multiple comparisons between groups. A p value of 0.05 or less was used as the level of significance in all statistical tests.

RESULTS

The number and severity of ulcers seen in the control animals was highly consistent with previous studies employing cold-restraint stress from this laboratory (14,15).

Analysis of the gastric pathology data revealed that both the mean number of ulcers and mean cumulative length per rat were significantly different across groups [H(10)=49.7 and 43.4 respectively, $p<0.001$ in each case, Kruskal-Wallis test]. Specifically, buspirone demonstrated opposing effects on stress-induced gastric pathology, with low doses resulting in significant ulcer attenuation while higher doses produced increasingly severe pathology. Only the middle dosage of 3.0 mg/kg did not result in pathology data significantly different from controls, despite the apparent increase in ulcer severity in this group.

The DA receptor blocker haloperidol facilitated stress ulcerogenesis, in contrast to the DA agonist apomorphine (Table 1), demonstrating marked ulcer attenuation. Haloperidol pretreatment was found to abolish and partially reverse the attenuating effect of low dose buspirone (1.0 mg/kg) on gastric pathology. As well, the ulcerogenic effect of a higher dose of buspirone (10.0 mg/kg) was partially reduced after combination with apomorphine. Reversing the order of the injections (apomorphine pretreatment) resulted in further decreases in gastric stress lesions, producing pathology that was not statistically different from controls.

DISCUSSION

Most notable from the present results are the opposite effects on ulceration seen between low and high doses of buspirone. Consistent with the protective role of DA against stress-induced ulceration (5, 9, 14, 15), haloperidol facilitated, and apomorphine greatly reduced ulcer formation. That haloperidol was able to block the attenuating effect of low dose buspirone (1 mg/kg) might well reflect a DA ergic basis for buspirone's action at this dose. Apomorphine partially reduced the ulcerogenic action of high dose buspirone (10 mg/kg), and to a greater extent when injected first. If the two drugs were acting through related mechanisms, one might expect the effect of the first drug injected to predominate. This however, was only partly true. Possibly, a longer pretreatment time (than the 40 min used) for apomorphine, would result in pathology ratings more similar to the apomorphine-alone group. Conversely, the lack of complete blockade of the buspirone effect in this group suggests that other mechanisms may be involved in the high dose effect of buspirone on stress ulcers. The fact that these higher doses produced more severe gastric pathology than haloperidol alone (a cataleptic dose), also indicates that DA antagonism alone was insufficient to account for the ulcerogenic effect. In any event, the results do not rule out a possible role for DA mechanisms in the action of buspirone at low as well as high doses.

Other studies have also suggested opposite actions of high vs. low doses of buspirone, particularly in relation to DA systems (16,17). In general, low doses of buspirone (effective in anticonflict situations) produce effects indicative of DA agonist activity, whereas higher doses result in changes typical of DA antagonism. Buspirone (1.0 mg/kg, SC) has been shown to reverse neuroleptic-induced catalepsy, as does apomorphine (13). In rats with unilateral 6-OHDA lesions of the substantia nigra, buspirone induced contralateral rotation, similar to but less pronounced than apomorphine, in a dose-related manner up to 2.5 mg/kg, SC, with higher doses causing hypoactivity (16). Anticonflict behavior (increased punished responding) has also been observed in rats following buspirone (5 mg/kg, PO), while the same dose given intraperitoneally caused a cessation of responding (17). On the other hand, elevation of striatal DOPAC (DA metabolite) levels, reflective of DA antagonism, has been reported following buspirone from 2.5–20.0 mg/kg, IP in the rat (16). In addition, buspirone increased the firing of DA neurons in the substantia nigra (16,17), as well as the ventral tegmental area (16). Such a shift in buspirone's action, particularly at the doses cited above, fits very well with the observed changes in stress ulcer development.

Recent studies, however, have demonstrated effects of buspirone on systems other than dopamine. More sensitive in vivo binding techniques have shown buspirone to affect ^{3}H-benzodiazepine binding, yet benzodiazepine antagonists fail to block the anticonflict actions of buspirone (17).

Buspirone has also been reported to supppress both the spontaneous and evoked activity of serotonergic (5-HT) dorsal raphe neurons (20). Some studies have reported changes in 5-HT_1, and others in 5-HT_2 receptor binding (17). This is of interest in light of suggestions that serotonergic systems may be involved in conflict-related behaviors (2, 3, 20), as well as the data indicating a possible role for the raphe nuclei in stress-induced gastric ulcers (10).

Despite suggestions that dopaminergic mechanisms may be involved in the etiology and expression of anxiety (18), the concept has emerged that buspirone may act as a midbrain modulator (2) whose anxiolytic properties reflect the simultaneous changes in several neurochemical systems (which include DA, 5-HT, and GABA-ergic systems). The present data implicating DA transmission in some of the effects of buspirone similarly cannot rule out the possibile influence of other systems on stress ulcer development.

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