Pharmacology Biochemistry & Behavior, Vol. 34, pp. 349–353. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Effects of Buspirone on Plasma Catecholamines, Heart Rate, and Blood Pressure in Stressed and Nonstressed Rats

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Received 19 December 1988

TAYLOR, J., N. HARRIS, M. KRIEMAN AND W. H. VOGEL. *Effects of buspirone on plasma catecholamines, heart rate, and blood pressure in stressed and nonstressed rats.* PHARMACOL BIOCHEM BEHAV **34**(2) 349–353, 1989.—The influence of buspirone upon plasma catecholamine levels, heart rate, and mean arterial blood pressure was studied in stressed and nonstressed rats. Measures were obtained directly via indwelling aortic catheters. Drug or vehicle were given acutely (10 mg/kg, IP) or twice a day for 10 days (10 mg and 20 mg/kg, SC). In nonstressed rats, a single dose of buspirone increased markedly plasma norepinephrine and epinephrine levels and decreased significantly heart rate with no effect on blood pressure. During stress, stress-induced increases in catecholamine levels were further elevated by the drug, whereas stress-induced increases of heart rate and mean arterial blood pressure were reduced. In chronically-pretreated rats, the effects of buspirone were similar to those observed after an acute injection. These effects of buspirone on plasma catecholamines are very different from those seen with other anxiolytics, whereas effects on heart rate and blood pressure are more similar.

Stress Buspirone Rat Catheterized Catecholamines Blood pressure Heart rate

EXPOSURE of rats to immobilization characteristically produces a variety of well-known stress responses (1, 2, 6, 8), including elevations of heart rate, mean arterial blood pressure, and plasma levels of the catecholamines, norepinephrine and epinephrine (HR, MAP, CA, NE, EPI). Some of these stress-induced changes are significantly reduced or antagonized by ethanol and anxiolytics such as diazepam or alprazolam (1, 3, 6, 13, 14). Thus, it can be suggested that part of the anxiolytic action of these drugs is a reduction and normalization of certain stress-induced biochemical and physiological changes.

Buspirone is a novel anxiolytic which differs structurally, pharmacologically, and clinically in many aspects from the established anxiolytics (4, 5, 10). Because of this unique profile, it was of interest to examine the effects of buspirone upon stress-induced changes in plasma CA levels, HR, and MAP in the conscious aortic-catheterized rat. Thus, we studied the effects of both acute and chronic dosing with buspirone on above parameters in stressed and nonstressed rats.

METHOD

Two separate experiments were performed. In Experiment one, nonstressed or stressed rats were tested twice: once with buspirone and once with vehicle (saline) following a counterbalanced cross-over design. Experiment two was designed to study the effects of repeated buspirone treatment for 10 days preceding the stress test. Rats chronically treated with buspirone or vehicle were tested twice: first under stress conditions and, 24 hours later, under nonstress conditions. For both experiments, procedures for catheterization, stress induction, HR and MAP measurement, blood sampling, and catecholamine assay were identical.

Sprague-Dawley male rats, 300 to 380 g, were obtained from Ace Breeding Laboratories, Boyerstown, PA, and allowed to acclimate in our vivarium (individually housed, Purina rat pellets and water ad lib, 23 to 24°C, 12 hr light/dark) for at least 5 days before surgery or initiation of any pretreatments. After acclimation, rats in Experiment one were used immediately for surgery and stress testing and given buspirone only once (10 mg/kg, IP). Rats in Experiment two were randomly divided into two groups. According to group assignment, rats were given buspirone (10 mg/kg a.m. and 20 mg/kg p.m., SC) or vehicle (1.0 ml/kg SC a.m., and 1.0 ml/kg SC p.m.) daily for seven days before surgery. This regimen was continued on the day of surgery, during the 48-hr postoperative recovery period, and thereafter, so that initial

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TABLE 1

EFFECTS OF BUSPIRONE OR SALINE ON PLASMA CATECHOLAMINES, HEART RATE, AND BLOOD PRESSURE IN NONSTRESSED RATS

	Minutes				
	−15	0	5	30	60
Norepinephrine (pg/ml)					
Saline	79 ± 13	99 ± 15	94 ± 13	67 ± 6	103 ± 13
Buspirone	80 ± 19	201 ± 30*	230 ± 43*	187 ± 46*	133 ± 14
Epinephrine (pg/ml)					
Saline	67 ± 14	61 ± 11	63 ± 3	37 ± 8	35 ± 5
Buspirone	59 ± 17	350 ± 56*	225 ± 59*	204 ± 77*	133 ± 40
Heart rate (bpm)					
Saline	355 ± 11	369 ± 11	372 ± 21	343 ± 7	377 ± 16
Buspirone	357 ± 11	272 ± 20*	272 ± 30*	294 ± 41*	283 ± 29*
Blood pressure (mmHg)					
Saline	92 ± 3	92 ± 4	90 ± 3	92 ± 3	91 ± 3
Buspirone	91 ± 2	84 ± 1	85 ± 2	88 ± 2	93 ± 4

Means ± sem, N = 5. Rats received buspirone (10 mg/kg IP) or saline just after the −15-min readings; rats remained at rest in their home cages during entire 75-min test period.
*$p<0.05$ as compared to saline control.

testing (stress) coincided with the tenth morning of chronic pretreatment and the second testing (nonstress condition) coincided with the eleventh consecutive morning dose of buspirone or vehicle. Repeated drug administrations were administered subcutaneously; however, the morning test-day dose was given intraperitoneally in accordance with the standard test protocol.

Catheters were constructed and implanted as described previously (1,6) with minor modifications. Briefly, a 4-cm length of teflon tubing (0.31 mm i.d., 0.62 mm o.d.) was heat-fused to a 30-cm length of polyethylene tubing (0.58 mm i.d., 0.97 mm o.d.). Just above its junction with the teflon tip, the polyethylene tubing was softened by immersing in boiling water and formed into a (7 mm i.d.) coil of 1.5 turns, thus providing shock absorbancy and making the catheter U-shaped. Rats were anesthetized with ketamine and acepromazine (100 + 10 mg/kg IP). Catheters were filled with heparinized saline (100 U/ml). A midline abdominal incision was made, the viscera were retracted, and the coiled part of catheter was anchored to the left psoas muscle with one silk suture. The teflon tip was cut to appropriate bevel and length. While occluding blood flow with finger pressure, a small incision was made in the aorta, and the teflon tip was inserted. Catheters were exteriorized via a skin hole in the back of the neck; a length of about 3 cm, sealed at the end with a stainless steel pin, was allowed to remain outside the rat. Rats were tested twice, once 48 hr postoperatively, and again 72 hr postoperatively; this procedure is important for proper measurement of plasma CA's and allows using each rat as its own control, thus substantially reducing the number of animals necessary. With this method, a minimum of 5 animals has been found to be sufficient to obtain valid results.

Before testing, catheters were attached to a longer length of polyethelene tubing so that cardiovascular parameters could be monitored and blood could be withdrawn for catecholamine assay without disturbance to, or even notice by, the rat. HR and MAP were monitored via Gould P23XL pressure transducers, and a Grass 78P polygraph. For each timepoint, cardiovascular measures were obtained and then the catheter was momentarily disconnected from the transducer while blood was withdrawn for CA assay. After establishing baseline (−15 min) values for MAP and HR and obtaining bloods for baseline NE and EPI, rats were dosed with saline or buspirone. In nonstressed rats, measures were taken at the indicated times. In stressed rats, fifteen minutes after dosing, values for the 0 min timepoint were obtained. Rats were then stressed by immobilization in the prone position. This procedure involves taping the four legs of the animal to the laboratory bench. After values for the 5- and 30-min timepoints were obtained, rats were released and returned to their home cages. Rats were allowed to rest for 30 min, the final (60 min) values for MAP and HR were recorded, and the final (60 min) blood samples for the NE and EPI assay were obtained.

Buspirone hydrochloride (a gift from Bristol-Myers Company) was dissolved in physiologic saline; doses are expressed as mg/kg free base. Dose volumes were always 1.0 ml/kg. Blood samples (about 0.2 ml) were drawn into syringes containing a solution of EGTA and glutathione, transferred immediately to cooled conical centrifuge tubes, and centrifuged; plasmas were drawn off and stored at −70°C until assay. The concentrations of NR and EPI in plasma were determined by radioenzymatic analysis (Cat-A-Kit®). The intraassay variance for norepinephrine and epinephrine basal levels was 6.8% and 9.9% and for stress levels 4.1% and 6.8% respectively. Results are expressed as means ± sem. The significance of differences between means was assessed with repeated measures analyses of variance followed by the Newman-Keuls' test.

RESULTS

The effects of saline or buspirone on plasma CA's, HR, and MAP in nonstressed rats are shown in Table 1. In both saline and buspirone tests, mean baseline (i.e., −15 min) values were the same. Injection of saline produced no effect on any of the parameters measured. Injection of buspirone increased plasma NE and EPI levels significantly by 2.5- to 6-fold and decreased significantly HR by about 30 percent. MAP was essentially unaffected by the drug. Effects reached maximum within 20 min after injection and, except for the bradycardia, diminished within 60 min.

TABLE 2

EFFECTS OF BUSPIRONE OR SALINE ON PLASMA CATECHOLAMINES, HEART RATE, AND BLOOD PRESSURE IN STRESSED RATS

	Min Before/After Beginning Stress				
	−15	0	5	30	60
			Stress		
Norepinephrine (pg/ml)					
Saline	130 ± 34	133 ± 28	551 ± 66*	539 ± 75*	209 ± 35*
Buspirone	82 ± 17	294 ± 72	1429 ± 170†	1113 ± 192†	262 ± 46
Epinephrine (pg/ml)					
Saline	135 ± 41	131 ± 43	913 ± 193*	964 ± 68*	149 ± 22
Buspirone	77 ± 18	560 ± 159	2304 ± 458†	1576 ± 306†	324 ± 26
Heart rate (bpm)					
Saline	369 ± 21	414 ± 20	530 ± 8*	520 ± 9*	467 ± 27*
Buspirone	385 ± 15	308 ± 19†	460 ± 18†	433 ± 20†	343 ± 31†
Blood pressure (mmHg)					
Saline	101 ± 3	115 ± 5	129 ± 5*	120 ± 5*	110 ± 6
Buspirone	97 ± 3	95 ± 4†	99 ± 2†	107 ± 4†	107 ± 4

Means ± sem, N = 5 to 7. Rats received buspirone (10 mg/kg IP) or saline just after the −15-min readings, were immobilized just after the 0-min readings, and were released from immobilization and returned to their home cages just after the 30-min readings.

*$p<0.05$ as compared to −15 min.

†$p<0.05$ as compared to saline control.

The effects of saline or buspirone on plasma CA's, HR, and MAP in stressed rats are shown in Table 2. When rats received saline, immobilization stress produced the expected increases in plasma CA's, HR, and MAP. After immobilization and return to the home cages, values for all parameters tended to return toward baseline. When rats received buspirone, stress-induced increases in plasma CA's were much greater (levels were nearly 3-fold greater as compared to saline treatment) but stress-induced increases in HR and MAP were significantly antagonized and reduced.

The effects of repeated saline or buspirone administration on plasma CA's, HR and MAP in nonstressed rats are shown in Table 3. Saline had no effect, whereas buspirone increased plasma catecholamine levels and decreased heart rate with no effect on

TABLE 3

EFFECTS OF BUSPIRONE OR SALINE ON PLASMA CATECHOLAMINES, HEART RATE, AND BLOOD PRESSURE IN NONSTRESSED RATS AFTER CHRONIC PRETREATMENT

	Minutes				
	−15	0	5	30	60
Norepinephrine (pg/ml)					
Saline	366 ± 64	415 ± 91	413 ± 53	402 ± 130	381 ± 119
Buspirone	387 ± 69	1000 ± 187*	795 ± 143*	724 ± 90*	552 ± 84
Epinephrine (pg/ml)					
Saline	329 ± 101	359 ± 86	543 ± 129	393 ± 122	335 ± 113
Buspirone	256 ± 57	1516 ± 222*	1180 ± 166*	943 ± 95*	606 ± 70
Heart rate (bpm)					
Saline	389 ± 20	430 ± 21	445 ± 31	424 ± 18	422 ± 24
Buspirone	402 ± 16	344 ± 16*	334 ± 13*	332 ± 20*	324 ± 18*
Blood pressure (mmHg)					
Saline	99 ± 5	102 ± 4	98 ± 4	103 ± 6	102 ± 4
Buspirone	97 ± 2	89 ± 5	90 ± 4	93 ± 4	99 ± 6

Means ± sem, N = 3 to 8. Rats received buspirone (10 mg/kg IP) or saline just after the −15-min readings; rats were allowed to remain at rest in their home cages during entire 75-min test period.

*$p<0.05$ as compared to saline control.

TABLE 4

EFFECTS OF BUSPIRONE OR SALINE ON PLASMA CATECHOLAMINES, HEART RATE, AND BLOOD PRESSURE IN STRESSED RATS AFTER CHRONIC PRETREATMENT

	Min Before/After Beginning Stress				
	−15	0	5	30	60
			Stress		
Norepinephrine (pg/ml)					
Saline	253 ± 61	296 ± 45	1464 ± 268*	989 ± 113*	676 ± 120*
Buspirone	312 ± 43	775 ± 148†	2843 ± 298†	2246 ± 195†	1007 ± 140
Epinephrine (pg/ml)					
Saline	276 ± 97	431 ± 170*	2378 ± 372*	1859 ± 243*	823 ± 172*
Buspirone	312 ± 56	1264 ± 179†	5290 ± 515†	4346 ± 504†	1272 ± 158
Heart rate (bpm)					
Saline	436 ± 21	418 ± 12	509 ± 13	491 ± 16	482 ± 17
Buspirone	386 ± 12	304 ± 9†	442 ± 9†	390 ± 12†	351 ± 20†
Blood pressure (mmHg)					
Saline	104 ± 4	107 ± 2	111 ± 4	111 ± 4	113 ± 4
Buspirone	103 ± 3	99 ± 5	103 ± 4	104 ± 4	106 ± 2

Means ± sem, N = 5 to 9. Rats received buspirone (10 mg/kg IP) or saline just after the −15-min readings, were immobilized just after the 0-min readings, and were released from immobilization and returned to their home cages just after the 30-min readings.

*$p<0.05$ as compared to −15 min.

†$p<0.05$ as compared to saline control.

MAP. Table 4 shows the effects of repeated buspirone administration on these 4 parameters in acutely-stressed rats. Stress alone increased plasma CA's, but not HR and MAP. Buspirone raised stress-induced plasma CA increases even more, whereas stress-induced increases in HR were reduced. No effect on MAP was noted. Baseline values in the repeatedly-pretreated animals (Tables 3 and 4) were higher than those seen in the acute animals (Tables 1 and 2) indicative of the fact that chronic injections were quite stressful to these animals.

DISCUSSION

It is important to study the effects of anxiolytics under both stress and nonstress conditions since the actions of anxiolytics depend very much on the situational conditions. The therapeutic action of anxiolytic agents often becomes apparent only in those tests which include a stress. For example, moderate doses of alcohol, diazepam, or alprazolam exert no major effects on plasma catecholamine levels or blood pressure in resting animals (1–3, 6, 13, 14). In stressed animals, however, the effects of alcohol, diazepam, or alprazolam are distinctly different. Here, stress-induced increases in plasma catecholamine levels and blood pressure are markedly reduced by the above agents (1–3, 6, 13, 14).

For buspirone, plasma catecholamine levels were increased in both the resting and stressed rat. In contrast, heart rate was significantly reduced in both the resting and stressed animals. Blood pressure was unaffected by the drug in nonstressed animals but could be reduced during stress. These effects were quite similar in animals receiving the drug for the first time or for a period of 10 days.

A comparison of the effects of buspirone with those of ethanol and diazepam or alprazolam in nonstressed and stressed animals shows the following. While buspirone consistently increased plasma catecholamine levels in nonstressed and stressed rats, all the other drugs have little effect on plasma catecholamines in resting rats but strongly reduce or antagonize the stress-induced increases in these biochemicals (13,14). The cardiovascular changes observed in buspirone-treated rats are also different from those observed in rats treated with other drugs. In the nonstressed rat, buspirone markedly reduced heart rate, whereas all the other drugs increase heart rate (1,6). In the stressed rat, buspirone substantially reduced the stress-induced increases in heart rate and blood pressure. The other anxiolytics also reduce stress-induced increases in heart rate and blood pressure but their effects appear to be less marked than those of buspirone (1,6).

In the study with chronically-pretreated rats, buspirone produced the same increased plasma CA levels and decreased HR just as seen in rats with acute treatment. However, a comparison of baseline values for heart rate, blood pressure and CA levels shows that they were higher in chronically-pretreated rats than in non-pretreated rats. The increased baseline values apparently blunted heart rate and blood pressure, but not plasma catecholamine responses during stress. Since higher baseline values were observed in both the rats receiving buspirone and the rats receiving saline, it appears that the stress from repeated SC injections, and not buspirone, was responsible for this effect. Interestingly, daily injections of buspirone did not prevent this apparent stress-induced increase in baseline values. These baseline data also reveal that the buspirone-induced elevations of CA levels are temporary since in the acute experiments plasma levels fell after one hr and since no compounding effects were seen in the repeated injection experiment.

The differences between the effects produced by diazepam or alprazolam compared to the effects produced by buspirone appear consistent with the different sites and modes of action reported for these drugs. The benzodiazepines facilitate gamma-aminobutyric acid (GABA) pathways and depress the firing of serotonergic,

dopaminergic and adrenergic cells in the brain, whereas buspirone exerts no influence upon GABA mechanisms, suppresses only serotonergic activity and increases dopaminergic and adrenergic activity (4,5). Thus, the increased plasma catecholamine levels observed in buspirone-treated rats may be related to increases in adrenergic nerve cell activity (4,5). It is possible to speculate that the buspirone-induced increase in catecholamine levels might have analogy to the clinical observation of lack of sedation and the increased activity or restlessness observed in some patients starting buspirone therapy (10).

It is of interest that buspirone increases sympathetic and adrenal medullary activities as evidenced by increased levels of NE and E and yet can reduce HR and BP at the same time. Thus, buspirone might have peripheral actions which antagonize the effects of the sympathetic and adrenal systems. It also seems remarkable that an anxiolytic agent at the dose employed in this study increases plasma levels of NE and E, chemicals whose levels, when elevated, are commonly regarded as markers for stress. Similar to its effects on plasma CA's, buspirone has also been shown to produce increased plasma levels of corticosterone, another "stress hormone" while diazepam did not (9). The increase in plasma catecholamine levels, in particular E, might be of concern if such increases can also be demonstrated in humans. Increased levels of E have been claimed to predispose to a variety of illnesses such as panic attacks, phobias, artherosclerosis, cardiac ischemic attacks and sudden death (7, 11, 12). Thus, chronic therapy with buspirone might be contraindicated in patients with such conditions.

ACKNOWLEDGEMENT

The financial support of this study by PHS Grant HA 06107 is gratefully acknowledged.

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