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The Pituitary–Adrenal Axis and the Different Behavioral Effects of Buspirone and Chlordiazepoxide

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McNAUGHTON, N., K. S. PANICKAR AND B. LOGAN. *The pituitary-adrenal axis and the different behavioral effects of buspirone and chlordiazepoxide.* PHARMACOL BIOCHEM BEHAV **54**(1) 51-56, 1996.—Benzodiazepines and the novel anxiolytic buspirone share a common capacity to relieve clinical anxiety but do not share any side effects. Anxiety releases stress hormones and, at moderate doses, anxiolytic benzodiazepines block this release. It is interesting, therefore, that buspirone and other 5-HT_{1A} agonists release stress hormones at moderate doses. Both the U-shaped dose-response curve seen with buspirone in some animal tests of anxiety and its slow onset of clinical action could be attributed to this release of stress hormones. Metyrapone (200 mg/kg), an inhibitor of 11-beta-hydroxylase, was used in the present experiments as a form of chemical adrenalectomy and was combined with administration of corticosterone (1 mg) to produce rats with presumed approximately normal corticosterone levels but no capacity to release endogenous corticosterone. This treatment reduced the difference normally observed in the effects of chlordiazepoxide (5 mg/kg) and buspirone (0.37 mg/kg) on a fixed interval schedule, particularly in the early part of the interval when release of behavioral inhibition would be expected to contribute most to the effects. These results are consistent with the previous suggestion of Johnston and File (8) that the anxiolytic action of buspirone may be counteracted by activation of the pituitary-adrenal axis. Corticosterone appears to be the most likely critical agent for this antagonist action in the present experiments, although CRF and ACTH are also possibilities. It is likely that there is a mutual functional opposition between endogenous anxiolytic factors and stress hormones.

Corticosterone Stress Anxiolytic Buspirone Chlordiazepoxide Metyrapone Fixed interval Pituitary Adrenals

NOVEL anxiolytic drugs such as buspirone and ipsapirone differ from classical anxiolytic drugs (benzodiazepines, barbiturates, meprobamate, etc.) both in their pharmacological site of action (5,23) and in the vast majority of their functional effects (6,25,26). Within the human literature it is probably safe to say that the sole obvious common action of these different types of drug is their capacity to reduce pathological anxiety.

Superficially, there is a difference in the clinical anxiolytic actions of the drugs in that buspirone, ipsapirone, and anxiolytic antidepressants such as imipramine all require about 2 weeks administration to achieve their effects. By contrast, the benzodiazepines are often held to have a virtually instantaneous anxiolytic action. However, particularly if Hamilton Anxiety Scale scores are used, the evidence is that 2 weeks of administration is required for the full anxiolytic effect of the benzodiazepines (28,30). One possible difference between classical and novel anxiolytics, then, is that the initial action of the benzodiazepines may not be specifically anxiolytic so much as euphoriant and muscle relaxant.

Superficial differences have also been noted in the preclinical pharmacology of the drugs. In particular tasks, or at higher doses in a variety of tasks, buspirone does not have an anxiolytic action [e.g., (4,16,18–22,24,27)]. The critical dose above which buspirone ceases to have its anxiolytic effects appears to be in the region of 1 mg/kg. Above this dose buspirone is known to release corticosterone [e.g., (2)], and it has been suggested (8) that this release, together with the failure of buspirone to block endogenous release of corticosterone, can account for its lack of anxiolytic effect at higher doses.

This preclinical pattern suggests an alternative account of the differences in clinical time course of the novel and classical anxiolytics to that suggested above. The initial anxiolytic effects of buspirone could be decreased by its release of corticosterone, while the initial anxiolytic effects of benzodiazepines

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could be enhanced by their blockade of anxiety-induced release of corticosterone. On this hypothesis, the effects of corticosterone would show tolerance or else its release would decrease over time, thus unmasking the anxiolytic effect of buspirone over a few days.

The idea that the central anxiolytic effect of buspirone is immediate, but masked by some antagonistic factor, is consistent with data on the control of hippocampal theta rhythm. We have developed, as a model of anxiolytic action, two tests of the control of theta rhythm that are neurophysiologically and neurochemically independent (11). All classes of drugs that have been shown to have a therapeutic effect in generalized anxiety disorder show a consistent pattern of action across these two tests (11,14), and no drug that shows this pattern has yet been shown not to be effective in treating generalized anxiety disorder. The effects of classical anxiolytics, buspirone and imipramine, are all immediate in these tests, have linear dose-response curves, and show no major changes in effect with repeated administration (32,33). Minor differences between benzodiazepines and buspirone on these tests dissappear when corticosterone is administered together with the benzodiazepines (11).

The idea that there is an anxiolytic-antagonist effect of corticosterone that decreases with repeated administration of buspirone is consistent with data we have obtained using the fixed-interval schedule. The fixed-interval schedule is of interest because it is unlike other tests that are sensitive to classical anxiolytic drugs in that it shows apparently qualitative rather than simply quantitative differences between buspirone and the benzodiazepine chlordiazepoxide (21). Further, the period of behavioral inhibition at the beginning of the fixed interval is of particular importance in relation to Gray's (7) theory of anxiety and anxiolytic action—and it is here that buspirone shows the greatest discrepency. We have shown that chronic administration prior to acquisition of the fixed-interval schedule essentially eliminates the differences between chlordiazepoxide and buspirone during the first week of acquisition of the schedule (34). Because, in the same animals, electrophysiological testing suggested that release of corticosterone had not diminished with time in the buspirone animals [and may have increased in chlordiazepoxide treated animals (33)], it seems most likely that the effects of corticosterone on some output target of the hippocampus (or some parallel circuit involved in the control of anxiety) had undergone tolerance.

The present experiment set out to test the possible involvement of corticosterone with anxiolytic action more directly. We administered metyrapone (MET, which would be expected to reduce the synthesis of corticosterone) together with exogenous corticosterone (CORT) in the hope that this would produce animals with relatively normal levels of corticosterone, but with no capacity to release corticosterone in response to stress or to buspirone. We elected not to use adrenalectomy because of the known effects of this treatment on hippocampal morphology.

Our predictions were that there would be no difference between MET + CORT animals and vehicle-injected controls when both of these groups received additional injections of saline; that the anxiolytic effects of chlordiazepoxide (CDP) would be reduced by MET + CORT because of an increase in circulating corticosterone levels (relative to control animals in which corticosterone release would normally be depressed by chlordiazepoxide); that an anxiolytic effect of buspirone (BUS) would be unmasked by MET + CORT because of a decrease in circulating corticosterone levels (relative to controls in which corticosterone levels would be increased by buspirone); and that MET + CORT + CDP animals would show essentially identical behavior to MET + CORT + BUS animals. The dose chosen for metyrapone (200 mg/kg) was one that pilot electrophysiological testing had shown produced effects similar to those of adrenalectomy, and the dose of corticosterone chosen (1 mg/kg) was one that reversed both the effect of metyrapone (17) and of adrenalectomy (1) on this electrophysiological test.

METHOD

Subjects

The subjects were 28 naive male Sprague-Dawley rats weighing 350–500 g at the beginning of drug treatment. They were obtained from the University of Otago animal breeding station and were housed four to a cage under natural incident illumination and received food and water ad lib for an acclimatization period of at least a week. They were gradually placed on a 23-h food deprivation schedule for 2 weeks before the start of the experiment. Water was available ad lib except in the testing chambers.

Drug Treatment

Buspirone (BUS), chlordiazepoxide (CDP), and metyrapone (MET) were each dissolved in saline (SAL) at concentrations required to give final injection volumes of 1 ml/kg. Corticosterone (CORT) was dissolved as 1 mg per 0.2 ml of propylene glycol (PG). All rats receiving metyrapone plus corticosterone were provide with saline drinking water to ensure maintenance of salt balance. Animals were assigned randomly to the following groups:

MET	CORT	SAL	$n = 4$
MET	CORT	BUS	$n = 5$
MET	CORT	CDP	$n = 5$
SAL	PG	SAL	$n = 4$
SAL	PG	BUS	$n = 5$
SAL	PG	CDP	$n = 5$

All animals were injected daily during the period of fixed-interval training at approximately the same time each day (and also as detailed below) according to the following schedule. Initially, either saline or metyrapone (200 mg/kg) was administered subcutaneously at the back of the neck as 1 ml/kg. One hour later, either propylene glycol or corticosterone (1 mg) was administered subcutaneously at the back of the neck. Thirty minutes later either buspirone, chlordiazepoxide, or saline was administered IP (for doses see below). Behavioral testing commenced 20 min after this last injection.

Apparatus

Twelve Camden Instruments operant chambers (24.5 × 22.5 × 23 cm) with grid floors were used to train and test all subjects. Each box was fitted with a food hopper and two retractable levers. In the present experiment, however, only one of the levers was extended into the chamber throughout the session. Illumination was provided by a 2.8 W house light. The experiments were controlled and data were collected by a BBC microcomputer using the SPIDER real time control system (Paul Fray, Cambridge, UK).

Pretraining

After 3 days of increasing periods of food deprivation and 2 weeks of 23-h food deprivation the rats were magazine

trained using a noncontingent Random Time 30-s schedule. On this schedule, all intervals between 0 and 60 s had equal probability of occurrence. The computer selected an interval using a random-number generator and then delivered a 45 mg reward pellet (Camden Instruments) at the end of the interval. A new interval was then selected for the next delivery. The lever was retracted from the box throughout magazine training. Subjects received a single session which lasted 30 min.

On the next day, the retractable lever was extended into the box. Food pellets were now available on a continuous reinforcement schedule contingent on lever pressing. On the first day wet mash was smeared on the lever. Rats that did not press the lever at least 150 times were given additional sessions of training at this point. Each session lasted 30 min and all subjects then received one session per day for 3 additional days.

On the next day all rats were given drugs according to their previously assigned groups. Due to an instructional error the doses of buspirone and chlordiazepoxide administered on this day were 33 mg/kg and 50 mg/kg, respectively, and the animals failed to respond on the lever. On the following day no drug was given and responding returned to normal levels. A rest period of 7 days (with continuing food deprivation) was given at this point to allow complete recovery from these high doses.

After the 7 day rest, 2 days of continuous reinforcement training were given without drugs, followed by 4 days with the previously assigned drugs. Chlordiazepoxide was given at 5 mg/kg and buspirone at 3.3 mg/kg. During these 4 days, responding in the MET + CORT + BUS group decreased markedly, in some cases to less than 20 bar presses per session.

On the next day only the MET + CORT + BUS group was run. They received no drug and responding recovered substantially. They were run for 2 further days at 0.37 mg/kg of buspirone (with MET + CORT), during which responding was at the predrug level of about 180 bar presses per session. They were then run for 2 days at 1.1 mg/kg buspirone and the performance of some rats again deteriorated. They then received an additional 3 days of testing at 0.37 mg/kg to ensure that performance would not deteriorate at this dose.

There were then two final days of continuous reinforcement training in which all drug groups were run with their assigned drugs and with CDP at a dose of 5 mg/kg and buspirone at a dose of 0.37 mg/kg. All rats achieved essentially the same level of responding of approximately 180 bar presses per session.

FI Schedule

The rats were then placed on an FI 60 s schedule for the remainder of the experiment (15 days). On this schedule, the first response that occurred after the passage of 60 s was rewarded with one pellet and then the interval was reset. Each subject was run in the same operant box, at the same time, each day for one 30-min session. For the first 10 days drug treatment was as in the last 2 days of continuous reinforcement training. For the last 5 days treatment with MET + CORT was discontinued.

Data Collection and Analysis

The computer recorded the bar presses of the rat and the time of each response from the start of the 60-s fixed interval. Responses were binned, depending on the time of their occurrence in 10-s bins (i.e., bin 1 contained responses between 0–10 s). The raw data were then subjected to a square root transform ($X' = SQRT[X + 0.5]$) to achieve normality of distribution (31) and then submitted to ANOVA. All effects involving days and bins were assessed for the presence of linear, quadratic, and cubic orthogonal polynomial components (29). The linear orthogonal polynomial extracted within ANOVA is identical to the slope of a linear regression fitted to the relevant means, and the higher order trends represent symmetrical curves with an increasing number of inflections as the order of polynomial increases [see (13); Fig. 1]. The data from days 1–10 and days 11–15 were submitted to separate analyses.

RESULTS

As noted under methods, in animals pretreated with MET + CORT, a dose of 1.1 mg/kg buspirone impaired performance on the continuous reinforcement schedule and a dose of 3.3 mg/kg produced a severe impairment (in some cases abolishing all responding). At a dose of 0.37 mg/kg MET + CORT + BUS rats appeared similar to the other groups, all of which appeared to show normal responding.

The results of the experiment are shown in Fig. 1. Compared to controls (SAL + PG + SAL), SAL + PG + CDP rats showed the expected increase in responding at all points in the fixed interval and SAL + PG + BUS rats showed a very modest overall increase with no change at the shortest intervals. The precise nature and size of these effects of both chlordiazepoxide and buspirone are virtually identical to a previous comparison of these same doses [(21); Experiment 1]. This suggests that the high dose of the drugs administered early in continuous reinforcement training produced no significant change in the drugs' effects.

During days 1–10 of the fixed-interval schedule MET + CORT was administered to the preassigned groups. MET + CORT + SAL rats were essentially indistinguishable from the SAL + PG + SAL controls (Fig. 1A), suggesting that the combination of metyrapone and corticosterone was achieving approximately normal levels of corticosterone. In the early part of the interval (when behavioral inhibition would be expected to be greatest) MET + CORT + BUS and MET + CORT + CDP showed a similar release in responding to each other. This is the portion of the curve where they have not previously been shown to have similar effects to each other. MET + CORT pretreatment both increased the anxiolytic effect of BUS and decreased the anxiolytic effect of CDP. The interaction of MET + CORT with drug condition was significant [MET + CORT × drug × bin, dev × dev × lin: $F(2, 2626) = 37.05, p < 0.001$].

With the exception of the SAL + PG + CDP rats, all groups showed a progressive decrease in responding in the early part of the FI over days of training. All groups, particularly the SAL + PG + CDP rats, showed a progressive increase in responding in the later part of the FI over days of training [Fig. 2, days × MET + CORT × drug × bin, lin × dev × dev × lin, $F(2, 2626) = 18.89, p < 0.001$].

From day 11, i.e., during days 11–15, MET + CORT pretreatment was not given. As can be seen from comparison of Fig. 1A with 1B, this did not greatly change the results obtained. There was continued learning, with a resultant increase in the overall effects of chlordiazepoxide and buspirone [days × drugs × bin, lin × dev × lin: $F(2, 1324) = 6.59$, $p < 0.001$], but this did not interact with previous MET + CORT treatment.

DISCUSSION

In general accordance with our predictions, the combination of metyrapone and corticosterone (a treatment that was

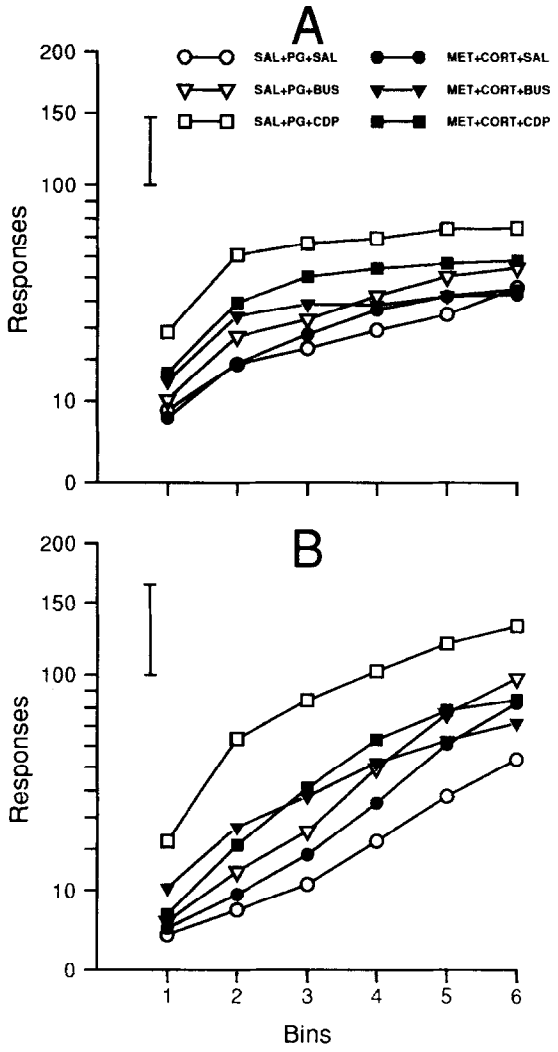

FIG. 1. Effects of the indicated combinations of metyrapone (MET, 200 mg/kg, SC), corticosterone (CORT, 1 mg, SC), buspirone (BUS, 0.37 mg/kg, IP), chlordiazepoxide (CDP, 5 mg/kg, IP), propylene glycol (PG), and saline (SAL) on responding on a fixed interval schedule. Bin 1 contains all responses made within the first 10 s of the FI, bin 2 the second 10 s, and so on. The nonlinear axis is the result of square root transform. The vertical bar represents 2 standard errors for between-group comparisons. (A) Days 1-10 of acquisition of the schedule. (B) Days 11-15, for which pretreatment with MET + CORT was discontinued.

intended to stabilize corticosterone levels) reduced the differences between the effects of chlordiazepoxide and buspirone. Both chlordiazepoxide and buspirone were affected (in opposite directions) suggesting that the former may obtain part of its anxiolytic action through blocking stress-induced release of corticosterone, while the latter may have its anxiolytic action reduced through its release of corticosterone.

Some caution is warranted with this conclusion.

First, due to an administrative error, all anxiolytic-treated rats had received a single very high dose of the drug during the continuous reinforcement phase of the experiment. This is probably not a serious problem, however, as both qualitatively and quantitatively, the effects obtained on FI are essentially identical to those obtained previously in a comparison of the same doses [(21), Experiment 1].

Second, in the MET + CORT + BUS group, the initial buspirone dose proved too high, and this group of rats received both a titration of buspirone dose and additional, correctional, sessions of CRF training to bring them to the same level of responding as the other groups. It should be noted here that these rats did not appear different from the other groups on the two final days of continuous reinforcement training. More importantly, while the early titration of buspirone dose means we cannot be sure about the quantitative aspects of the later comparison between MET + CORT + CDP and MET + CORT + BUS, qualitatively we can see that the MET + CORT + BUS group show an increase in responding in the early part of the FI interval compared to SAL + PG + BUS as predicted.

Third, we did not measure corticosterone levels, nor did we obtain dose-response curves. We cannot be sure, therefore, that the dose of metyrapone we used was sufficient to produce a total inhibition of corticosterone synthesis. In the case of buspirone and chlordiazepoxide, prior dose-response curves (21) have shown a categorical difference between buspirone and chlordiazepoxide in terms of effects on responding in the early part of the fixed interval, which is obtained at all doses of both drugs. It is this difference that was eliminated in the present experiment. In the case of corticosterone, we used a dose that had previously been sufficient to reverse the effects of adrenalectomy without producing effects similar to an excess of corticosterone (1). Nonetheless, it is possible that the levels of corticosterone in the present experiment would have been equivalent to those normally obtained in response to stress. In the case of metyrapone, we used a dose that resulted in the predicted opposite changes in the effects of chlordiazepoxide and of buspirone, which were predicated on the loss of the capacity for endogenous release of corticosterone. Nonetheless, there is clearly room for a much more extensive study that varies doses of drug parametrically and measures levels not only of corticosterone but also of CRF and ACTH as well.

While it is simplest to attribute the present results to a stabilization of corticosterone levels, it is also possible that they result from changes in CRF and ACTH. If the achieved level of corticosterone were unusually high, this could have blocked the normal release of CRF and ACTH by buspirone and could have reduced CRF and ACTH levels to a point where chlordiazepoxide could not reduce their release further. This elimination (and, hence, stabilization) of CRF and ACTH levels could, therefore, account for the results rather than stabilization of corticosterone levels. The only evidence against this is the markedly depressant effect of buspirone in the continuous reinforcement condition, which could be attributed to a release of CRF that was not counterbalanced by an accompanying release of corticosterone. For all of these reasons measurement of CRF and ACTH levels would be desirable in future experiments of this type.

The lack of change in the results when MET + CORT was discontinued is, at first sight, surprising. However, we have argued elsewhere (9,12) that it is only during the initial acquisition of aversive schedules that anxiety is involved in the control of behavioral inhibition. Certainly, a continued behavioral effect on performance more than a week after discontinuation of acquisition drug treatment is also obtained with CDP [(9), Experiment 4].

The capacity of MET + CORT to generate an anxiolytic

effect of buspirone appears limited to the early part of the fixed interval. If this proves a robust phenomenon it could be of considerable theoretical interest. Classical anxiolytic drugs appear to both increase responding in general and decrease behavioral inhibition. Given the learning theoretical basis for Gray's (7) theory of anxiolytic drug action on a Behavioral Inhibition System, it would be expected that the specifically anxiolytic effects of drugs should be related to action on the early, inhibited, section of the fixed interval. It may be, then, that MET + CORT is unmasking an anxiolytic action of buspirone, and the failure to produce a similar effect on responding in the later part of the fixed interval is because changes in this relate to side effects of the classical anxiolytic drugs rather than their main effects.

If they can be taken at face value, the present results suggest that the differences between buspirone and chlordiazepoxide on tests of anxiety can be at least partially accounted for by the opposite effects that each has on corticosterone

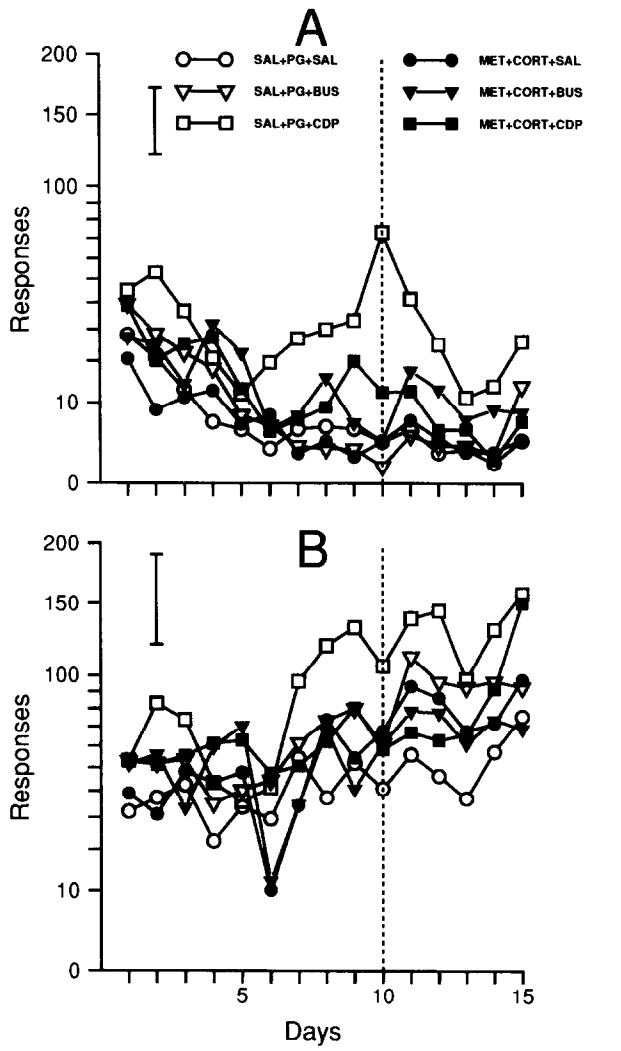

FIG. 2. As for Fig. 1, except that A plots responses for bin 1 only across days of testing and B plots responses for bin 6 only across days of testing. The vertical dashed line marks the discontinuation of MET + CORT pretreatment.

levels or on some other aspect of the pituitary-adrenal axis. It is important to note that this does not imply a direct pharmacological antagonism between pituitary-adrenal hormones and either drug. This would be quite unlikely, given the very different pharmacologies of the classical and novel anxiolytics. Rather, it appears most likely that the hormones produce a functional antagonism at some point in a final common path downstream from the different sites of direct action of the different anxiolytics.

There are a number of data that are consistent with this view. First is the fact that in our electrophysiological tests of hippocampal control, corticosterone does not antagonize the critical effects of chlordiazepoxide (11), although it does make the effects of chlordiazepoxide similar to those of buspirone. In these electrophysiological tests the direct actions of the anxiolytics are on nuclei afferent to the septohippocampal system rather than directly on the hippocampus itself. Given the high number of corticosterone receptors in the hippocampus, it is possible that it represents the final common path for the corticosterone-sensitive behavioral effects. Second, there are behavioral tests in which chlordiazepoxide and buspirone produce similar effects and in which buspirone has a linear rather than U-shaped dose-response curve: rearing in a low stress open field (18) and spatial navigation in the Morris Water Maze (15). Given the use of cold water in the latter test, and the capacity for this to release corticosterone, it seems most likely that the effects of the anxiolytics on these tests are not susceptible to corticosterone. This could occur if the effects of the anxiolytics on these tests depend on different output pathways to those that are corticosterone sensitive—again suggesting that the action of corticosterone is downstream from the direct sites of action of the anxiolytics.

It seems unlikely that corticosterone would produce its functional antagonism by an independent anxiogenic action, which simply subtracted from the anxiolytic effect of buspirone, because, if anything, its direct actions appear to be anxiolytic within the physiological range (3). Nor can most of the present results be easily explained via changes in ACTH or CRF, which would not be expected to be normalized by the metyrapone/corticosterone combination unless very high levels of corticosterone were achieved. Indeed, it seems likely, as noted above, that the problems encountered with continuous reinforcement training in the MET + CORT + BUS animals could be due to unusually high levels of CRF, resulting from a failure of the normal negative feedback of corticosterone on CRF release. However, careful parametric studies would be needed to determine whether the different effects that buspirone and chlordiazepoxide have on food intake contribute to the present pattern of results.

Overall, the present study suggests (but in no way proves) that some of the observed behavioral differences between novel and classical anxiolytics are due to their different interactions with the pituitary-adrenal axis or with related hormonal systems. This suggests that endogenous anxiolytic systems and endogenous stress systems may be functionally opposed. The most important finding is that a pharmacological pretreatment (metyrapone + corticosterone), which leaves control behavior intact and retains at least some of the anxiolytic action of a classical anxiolytic, renders the effects of buspirone on the fixed-interval schedule similar to the classical anxiolytic. In this, MET + CORT is like (although not as effective as) long-term pretreatment with the anxiolytics before acquisition of the fixed interval. In turn, this suggests that the anomalous actions of buspirone on a number of behavioral screening tests (of which fixed interval appeared a

particularly troublesome example) do not require us either to conclude that buspirone is not inherently anxiolytic or to conclude that the theoretical basis of the tests is seriously flawed.

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