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Changing Concepts of the Biochemical Action of the Anxioselective Drug, Buspirone

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ABSTRACT

Taylor, D.P., L.E. Allen, J.A. Becker, M. Crane, D.K. Hyslop, and L.A. Riblet: Changing concepts of the biochemical action of the anxioselective drug buspirone. Drug Dev. Res. **4**:95–108,1984.

Clinical trials have demonstrated that buspirone (Buspar™) is effective in the treatment of anxiety with efficacy and dosage comparable to diazepam or clorazepate. Buspirone is chemically distinct from the benzodiazepines as well as other psychoactive drugs. More importantly, buspirone presents a clinical pharmacologic profile which is "anxioselective"; that is, it relieves anxiety without the accompanying ancillary properties of benzodiazepines (sedation, muscle relaxation, seizure control). Biochemical investigations have not conclusively identified any direct interaction of buspirone with the benzodiazepine-γ-aminobutyric acid (GABA)-chloride ionophore complex. It has been known that buspirone possesses some pharmacologic properties that are shared by dopamine antagonists. However, these properties are not characteristic solely of this class of agents. In contrast to dopamine antagonists, buspirone does not produce catalepsy. In fact, buspirone reverses catalepsy induced by dopamine antagonists. Recent investigations have demonstrated that chronic administration of dopamine antagonists increases dopamine receptor binding in experimental animals. Chronic treatment with buspirone does not have this effect. In conjunction with other observations, it has now become obvious that buspirone does not possess the postsynaptic dopamine antagonism characteristic of antipsychotic drugs. However, the mechanism by which buspirone alleviates the clinical manifestations of anxiety continues to be undefined.

Key words: buspirone, nonbenzodiazepine, anxioselective drug

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INTRODUCTION

Neurotic anxiety may produce such a level of apprehension that the patient is effectively crippled by the intensity of the emotion evoked. Antianxiety agents can ameliorate the debilitating symptoms of the disease, thereby facilitating problem solving and enabling the patient to cope with his life situation. Anxiety has been treated historically by agents with a sedative component to their action: belladonna, opiates, alcohol, barbiturates, antihistamines, propanediol carbamates, phenothiazines, benzodiazepines. Pharmacologic profiles of effective antianxiety drugs suggest that their anxiolytic actions are mediated by γ-aminobutyric acid (GABA). Until recently, it has been thought that antianxiety drugs must alter [^{3}H]benzodiazepine binding in vitro. In addition to sedation, the benzodiazepines possess anticonvulsant and muscle-relaxant properties. Moreover, this class of compounds interacts disastrously with alcohol or barbiturates and may produce physical dependence after long-term ingestion. The need for drugs that have fewer side effects, are more selective, and present a profile consistent with safety during protracted treatment has resulted in a continuing search for new antianxiety drugs. This search has led to the synthesis and evaluation of chemical compounds that possess no obvious homology with the benzodiazepines.

CLINICAL PROFILE OF BUSPIRONE

Buspirone (Buspar^{TM}, Mead Johnson Pharmaceutical Division, Evansville, IN) is one of a series of azaspirodecanedione psychotropic agents [Wu and Rayburn, 1973; Wu et al., 1972; Casten et al., 1980] that is structurally distinct from the benzodiazepines. Animal models of psychiatric disorders employed in the late 1960s at the time of buspirone's initial industrial evaluation suggested that the compound might have clinical utility as an antipsychotic agent free of the sedative and cataleptic liabilities common to the phenothiazine antipsychotics. Indeed, the clinical profile of buspirone was found to be devoid of these blemishes, but Sathananthan and co-workers [1975] were unable to demonstrate a clear antipsychotic effect. Even at high doses (mean of 1.5 g/day, mean duration of 25 days) any relief of antipsychotic symptomatology was equivocal. Detailed pharmacologic evaluations conducted subsequently demonstrated tranquilizing activity for buspirone and suggested it might be utilized in the treatment of anxiety.

Preliminary double-blind clinical trials in 56 adult psychoneurotic out-patients with a primary diagnosis of anxiety neurosis showed buspirone to be as effective as diazepam on a milligram basis in a variety of clinical rating scales for anxiety. The buspirone patients had side effects half as frequently as the diazepam and placebo patients [Goldberg and Finnerty, 1979]. A second double-blind study in 240 anxious outpatients again demonstrated clinical efficacy for buspirone and diazepam over placebo. Buspirone appeared to be more effective especially in reducing symptoms indicative of cognitive and interpersonal problems, including anger-hostility. In this study diazepam produced significantly more fatigue than either placebo or buspirone. The occurrence of fatigue in buspirone-treated patients could not be statistically distinguished from that in patients receiving placebo [Rickels et al., 1982]. A third study with 100 patients fulfilling the DSM-III criteria for generalized anxiety disorder confirmed that the improvement with buspirone was comparable to that obtained with diazepam. Moreover, diazepam treatment was associated with a markedly (fourfold) higher incidence of adverse reactions that significantly interfered with the therapeutic effect of the medication [Feighner et al., 1982]. No difference was evident in the therapeutic benefit obtained by 129 patients receiving either buspirone or chlorazepate, although 32% of those receiving the benzodiazepine felt their relief was due to counseling or changes in their life situation. Significantly, only 8% of the patients receiving buspirone felt their improvement was not drug related. Furthermore, the buspirone-treatment group had the lower incidence of side effects, with a particularly obvious lack of sedation [Goldberg and Finnerty, 1982].

The clinical side-effect profile of buspirone was examined by ten investigators in multicenter studies in over 1,200 patients receiving buspirone, placebo, or a benzodiazepine. Sedation, lethargy, and depression were significantly less with buspirone than with diazepam or clorazepate and were comparable to placebo [Newton et al., 1982]. The side effect profile of diazepam, but not buspirone, was adversely affected by the concomitant use of a variety of common medications (analgesic, antihistamine/vasoconstrictor, contraceptive, diuretic/antihypertensive, hormone, or sedative/hypnotic [Gershon, 1982]).

The possibility that buspirone, like the benzodiazepines, might produce functional impairment, either alone or in combination with alcohol, to the detriment of physical performance, was investigated in three separate studies with volunteer (normal) subjects with doses relevant to the clinical experience. Lader [1982; Bond and Lader, 1981] showed that acute buspirone did not interfere with complex coding tasks, whereas diazepam readily produced a decrement in performance. Mattila and his associates [1982; Seppälä et al., 1982] also showed that acute buspirone administration did not significantly modify actual skills in the performance of psychomotor tests. Lorazepam, another benzodiazepine, impaired psychomotor performance and concurrent ingestion of alcohol enhanced the deterioration of physical skills. In contrast, the combined objective effects of alcohol and buspirone on these skills were not greater than those of alcohol alone. In exceedingly sophisticated studies, Moskowitz and Smiley [1982] evaluated the performance of driving-related skills after acute and chronic (8 days) drug administration and in combination with alcohol on the ninth day. Diazepam substantially impaired skills performance without producing tolerance; rather, there was a suggestion of an extended duration of impairment. In marked contrast, buspirone treatment contributed to improved performance, to the extent that it could even offset some of the impairment due to alcohol.

Illicit use of sedative-hypnotics for their euphorient effects is common, and the abuse of the benzodiazepines has attracted increasing public concern. The abuse liability of buspirone was evaluated in comparison to diazepam, methaqualone, and placebo by 24 experienced, casual recreational sedative users in a double-blind crossover design. One interesting finding came when these "connoisseurs" were asked to estimate the "street value" of a "hit" of each of these drugs. The mean values assigned were $3.50 for 300 mg of methaqualone, $0.68 for 10 mg of diazepam, $0.24 for 10 mg of buspirone, and $0.23 for placebo. It was concluded that it would be unlikely for buspirone to be popular with the illicit drug users [Cole et al.,1982].

In summary, buspirone is structurally distinct from the benzodiazepines, but it shares their ability to relieve the clinical symptoms of anxiety. Buspirone is further distinguished by its anxioselectivity [Taylor et al., 1980], its lower incidence of adverse reactions, and its inability to produce psychological impairment alone or in combination with alcohol. Finally, buspirone appears to have little abuse potential.

PRECLINICAL PROFILE OF BUSPIRONE

Comparison to Benzodiazepines

As mentioned above, at the time of buspirone's invention the available animal models of psychiatric disorders suggested potential clinical utility as an antipsychotic agent free of sedative and extrapyramidal side effects. Specifically, buspirone was active in the inhibition of conditioned avoidance responding [Allen et al., 1974]. At the time this procedure was believed to be predictive of major tranquilizer activity. However, the potency of the benzodiazepines in this procedure is significantly correlated with their clinical efficacy as anxiolytic minor tranquilizers [Snyder and Enna, 1975]. Thus, the inhibition of the conditioned avoidance response is, at best, a measure of general tranquilizing activity. That this activity might be mediated by inhibition of dopaminergic neurotransmission was suggested by buspirone's ability

to block apomorphine-induced emesis in dogs. However, it was clear that buspirone could be distinguished from the phenothiazines, chlorpromazine and perphenazine, by its inability to produce catalepsy, lack of sedative properties, and lack of α-adrenolytic activity [Allen et al., 1974].

The preclinical investigation of the tranquilizing properties of buspirone was continued in a behavioral paradigm first described by Plotnikoff [1973]. Buspirone inhibited aggressive behavior ("taming") in rhesus monkeys in a manner similar to diazepam, but without the benzodiazepines' concomitant induction of ataxia [Tompkins et al., 1980]. It was, in fact, this signal result which led to buspirone's reintroduction into the clinic [Stanton et al, 1981]. With the ensuing success of buspirone in clinical trials of anxiolytic efficacy mentioned above, it became incumbent to investigate the ancillary properties of buspirone with special reference to similarities to and distinctions from other major antianxiety agents, chiefly the benzodiazepines.

Like other antianxiety agents, buspirone possesses tranquilizing activity in conditioned avoidance and taming paradigms mentioned previously, as well as the ability to release punishment-suppressed behaviors—e.g., eating in monkeys and drinking in rats in the case of the conflict paradigms developed by Geller and Vogel, respectively [Geller and Seifter, 1960; Vogel et al., 1971]— and to suppress footshock-induced fighting in mice [Riblet et al., 1982; Geller and Hartman, 1982; Hartman and Geller, 1981; Oakley and Jones, 1983]. Unlike the benzodiazepines, the anticonflict effect of buspirone is not prevented by the benzodiazepine antagonist Ro 15-1788 [Oakley and Jones, 1983] or CGS 8216 [Weissman et al., 1983, this volume]. Depending on the test paradigm, buspirone is effective at very low does, 0.5–2 mg/kg orally, equivalent to those seen for chlordiazepoxide or diazepam [see Eison and Eison, 1983, this volume]. Thus, these systems jointly predicted the clinical efficacy of buspirone in the treatment of anxiety states mentioned above.

Unlike the benzodiazepines, the ancillary properties of buspirone stand in marked contrast; indeed, it was this distinction which led to our coining the term "anxioselective" to describe buspirone's properties [Taylor et al., 1980]. Thus, buspirone possesses efficacy in animal models of anxiety and in clinical trials (like the benzodiazepines) and lacks sedation, lethargy, depression, detrimental interactions with concomitant medications, psychological or psychomotor impairment alone or in conjunction with alcohol, and potential for illicit abuse in humans. Moreover, its preclinical profile is consistent with a significant advantage over the existing benzodiazepine therapeutic modalities in side effects, safety, and abuse liability. These properties of buspirone have been described previously [Riblet et al., 1982], but they may be summarized in the following way.

Buspirone was found to be without effect (no protection at doses up to 400 mg/kg, p.o.) on convulsions produced in rodents by bicuculline, pentylenetetrazol, picrotoxin, and strychnine, as well as maximal electroshock seizures, whereas diazepam was active against all of these agents. Unlike most anxiolytics, buspirone does not decrease spontaneous motor activity in the rat at doses up to 100 mg/kg, p.o. Another clinically relevant indication of sedative activity is the ability of drugs to interact with subthreshold doses of central nervous system (CNS) depressants in order to block the righting reflex in rodents. In this regard, buspirone was at least 30-fold less potent than diazepam [Riblet et al., 1982], indicating the absence of hypnotic properties, a finding consistent with clinically observed actions [Goldberg and Finnerty, 1979, 1982; Rickels et al., 1982]. Moreover, ethanol and hexobarbital potentiated the lethality of diazepam, whereas buspirone was safer when administered in conjunction with these agents [Riblet et al., 1982]. Another activity associated with the benzodiazepines is the ability to induce muscle relaxation. Buspirone is significantly less potent than diazepam in producing motor incoordination as assessed using rodents in a rotating rod model [Riblet et al., 1982]. Further, buspirone produced effectively no muscle weakness when the ability of rodents to remain suspended from a horizontal bar was determined [Riblet et al., 1982]. While it is difficult to conduct studies of dependence potential or abuse liability in humans, several animal paradigms have been employed which have served to distinguish buspirone from

conventional anxiolytics. For instance, buspirone does not serve as a positive reinforcer for intravenous self-administration as a substitute for cocaine in rhesus monkeys [Balster and Woolverton, 1982]. In addition, the discriminative stimulus properties of buspirone differ from those of the benzodiazepine oxazepam and the barbiturate pentobarbital. In particular, rats trained to discriminate oxazepam from vehicle identified pentobarbital as oxazepamlike and buspirone as vehiclelike. In the converse experiment, animals trained to discriminate pentobarbital from vehicle-identified oxazepam as pentobarbitallike and buspirone as vehiclelike. Finally, rats could only be poorly trained to discriminate buspirone from vehicle. In this case, oxazepam and pentobarbital were not generally identified as either treatment. A compound such as buspirone that lacks the strong recognizable stimulus properties of oxazepam or pentobarbital is unlikely to be abused [Hendry et al., 1983]. In a rigorous investigation of possible induction of physical dependence, buspirone and diazepam were administered to rats for 22 days at 200 mg/kg, p.o. Chronic administration of compounds which are known to produce clinical dependence, such as morphine and barbiturates, will manifest this dependence in laboratory animals by producing a decrease in body weight upon withdrawal [Yanaura et al., 1975]. In this study, the diazepam-treated animals showed a significant withdrawal-induced weight loss typical to dependence-inducing agents, whereas the buspirone-treated animals exhibited a slight nonsignificant weight *gain* upon withdrawal [Riblet et al., 1982; see Fig. 1]. Thus, preclinically buspirone does not share the benzodiazepines' ability to control seizures, to produce sedation, to relax muscles, to potentiate the lethality or sedative activity of commonly used depressants, or produce drug dependence after chronic treatment.

It is now well accepted that clinically effective anxiolytics such as the benzodiazepines, propanediol carbamates, and barbiturates, as well as some potential agents under current development (tracazolate, CL 218,872, CGS 9896, PK 9184) achieve their action by alterations of binding at the receptor complex for GABA and benzodiazepines, which may also alter chloride anion permeability [Williams, 1983]. In view of the differential behavioral pharmacology of buspirone vis-à-vis conventional anxiolytics, it is not surprising that the compound is essentially devoid of in vitro interactions at this neurochemical locus. In particular, buspirone, its 5-hydroxylated metabolite, and its cleavage product 1-(2-pyrimidinyl)piperazine are devoid of affinity for [^{3}H]benzodiazepine binding sites in vitro (IC_{50} values greater than 100 μM[1] [Riblet et al., 1982; Yevich et al., 1982, 1983; Hirsch et al., 1982; Schoemaker et al., 1981]) or for GABA or picrotoxin binding sites [Riblet et al., 1982; Tunnicliff and Welborn, 1983, this volume; R.F. Squires, personal communciation]. Under some circumstances, preincubation with buspirone has altered GABA binding, but these effects are only poorly reproduced [Garattini et al., 1982, personal communication; Tunnicliff and Welborn, 1983, this volume; Weissman et al., 1983, this volume]. Very recently in vivo or ex vivo treatment with buspirone followed by [^{3}H]benzodiazepine has indicated that the compound can indirectly alter this complex (see Table 1) [Garattini et al., 1982; Oakley and Jones, 1983; Weissman et al., 1983, this volume]. However, it is accepted that this action may be correlated with direct anxiolytic activity mediated at some other site [Oakley and Jones, 1983; Taylor et al., 1982].

One candidate for such a site might have been the [^{3}H]adenosine uptake site on rat brain synaptosomes, where benzodiazepines have IC_{20} values as low as 5 nM. However, the IC_{20} for buspirone of 20,000 nM suggests that this mechanism is not relevant to the drug's anxiolytic action.[1] It is interesting to note that dopamine antagonists from various chemical families, such as trifluoperazine (phenothiazine), spiperone (butyrophenone), and sulpiride (benzamide), were even more potent than the benzodiazepines [Phillis and Wu, 1982].

[1]In this regard it is relevant to note that peak plasma levels in humans after a therapeutic dose of buspirone (20 mg orally) did not exceed 16 nM [Mayol et al., 1981, 1983; Gammans et al., 1982, 1983b]. For a behaving rodent preparation it has been observed that peak brain levels of buspirone after a 25 mg/kg oral dose are approximately 100 nM [Gammans et al., 1983a].

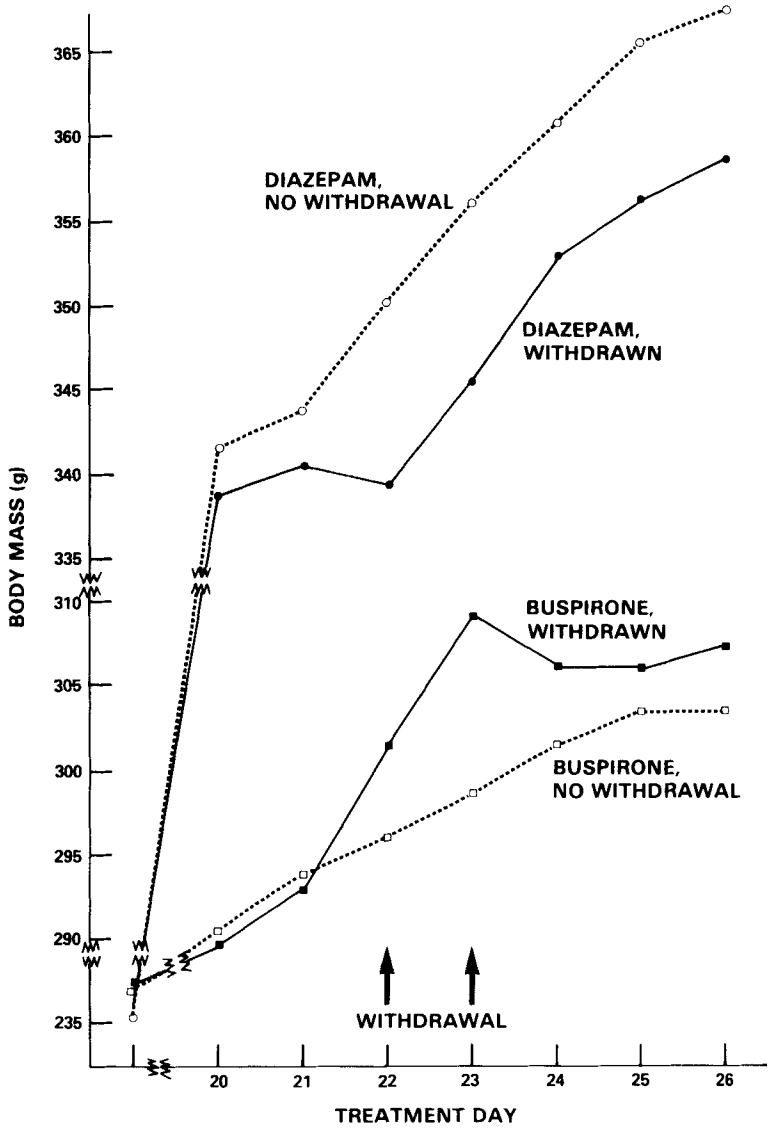

Fig. 1. Effect of drug administration, with or without withdrawal, on body weight. Groups of ten male Sprague-Dawley rats were individually caged with free access to lab chow and water. Two groups of animals received diazepam (in 0.5% methyl cellulose) and two groups received buspirone (in distilled water) orally on a twice-daily schedule (8:30 A.M. and 3:00 P.M.). This schedule began with 50 mg/kg for each drug (100 mg/kg/day total). Each day the dose increased 10 mg/kg until it reached a dose of 100 mg/kg twice daily (200 mg/kg/day total). On the 22nd day of the study, one group on each drug was withdrawn from drug, receiving vehicle instead. The withdrawn animals received four vehicle doses (indicated by arrows on the abscissa), and drug administration was reinstituted on the 24th day. Body mass was measured daily at 8:30 A.M. The average mass is plotted for each group as follows: diazepam, no withdrawal (——0——); diazepam, withdrawn (——●——); buspirone, no withdrawal (——□——); buspirone, withdrawn (—■—).

TABLE 1. The Effect of Anxiolytic Drugs on [^{3}H]Diazepam Binding In Vivo†

Drug treatment (dose, mg/kg, p.o.)	Percent specific binding in region		
	Cortex	Cerebellum	Hippocampus
Saline	23.7 ± 2.0	24.7 ± 1.7	24.4 ± 0.7
Buspirone (4)	28.0 ± 0.5**	23.9 ± 0.8	27.3 ± 0.9*
Diazepam (2)	23.8 ± 0.3	18.8 ± 1.2*	19.7 ± 0.9*

†Male Sprague-Dawley rats that had reversed day-night light cycles were dosed with vehicle or drug in groups of ten at two times the minimally effective dose for attenuation of punishment-suppressed responding [Taylor et al., 1982]; animals with normal day-night light cycles did not exhibit any change in [^{3}H]diazepam binding after buspirone treatment. Ten minutes later, each rat received 50 μCi [^{3}H]diazepam (85.3 Ci/mol, New England Nuclear) via the tail vein. Animals were sacrificed 1 min later and brain regions were frozen, stored at −80°C, processed as described by Williamson et al. [1978], and modified according to Weissman et al. [1983, this volume]. Briefly, each region was thawed, weighed, and homogenized by Polytron in 20 volumes of HEPES·KOH, pH 7.4. Two 250-μl aliquots were counted directly for total radioactivity present. Six 1,000-μl aliquots were incubated on ice for 30 min. Nonspecific binding was defined by the addition of 25 μl 250 μM diazepam to three of the aliquots. Following incubation, the aliquots were filtered under reduced pressure through Whatman GF/B filters. These were washed with 2 × 5 ml buffer, air dried, and placed in 10 ml scintillant for counting. The results are expressed as total binding less nonspecific binding, the quantity being divided by the total radioactivity present.

*$P < 0.05$ vs. saline (Student's t-test, two-tailed).

**$P < 0.10$ vs. saline (Student's t-test, two-tailed).

Another distinct site where the biochemical action of buspirone and the benzodiazepines might coincide is in the area of signal transduction, the production of intracellular second messengers. Buspirone does not alter basal adenylate cyclase activity and displays little ability to block the stimulation of the striatal enzyme by dopamine (IC_{50} greater than 100,000 nM [Cimino et al., 1983]. Paul and Skolnick [1982] have noted that benzodiazepines enhance potassium-induced, depolarization-coupled uptake of ^{45}Ca into synaptosomes. Preliminary experiments by these investigators have revealed a similar enhancement by buspirone, although this occurs at micromolar concentrations, but not with the dopamine antagonists chlorpromazine or haloperidol. The further relevance of these findings is an open question.

There have occasionally been suggestions that antianxiety drugs may act through serotonin receptors [Stein et al., 1973]. Recently, it has been suggested that buspirone may produce its effect by acting as a serotonin agonist [Hjorth and Carlsson, 1982]. For instance, buspirone administration results in the inhibition of spontaneous firing of serotonergic dorsal raphe neurons in the rat [C. P. VanderMaelen, personal communication; Eison et al., 1983]. Further, buspirone may produce at least one of the six characteristic traits of the serotonin syndrome [Eison et al., 1983; Hjorth and Carlsson, 1983]. Neurochemically, decreases in striatal levels of both 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) have been reported after buspirone administration [Hjorth and Carlsson, 1982]. Such changes are not seen for serotonin in the frontal cortex [McMillen and Mattiace, 1983a] or for 5-HIAA in the frontal cortex or hippocampus at 10 mg/kg [McMillen, personal communication; Garattini, personal communication]. That such effects may be directly mediated at the receptor level receives support from 5-HT_1 binding studies done in calf brain [Glaser and Traber, 1983], but not from rat brain [Riblet et al., 1982; Garattini, personal communication]. In fact, administration of buspirone to rats unilaterally lesioned in the medial forebrain bundle with 5,7-dihydroxytryptamine did not result in consistent rotational behavior [Eison et al., 1983]. Clearly, further studies are needed in order to establish the relevance and importance of serotonin receptor interactions in determining the therapeutic outcome of buspirone treatment.

Similarly, α-adrenergic receptors have been implicated in the reduction of anxiety by benzodiazepines [Redmond, 1977]. In vitro receptor binding, epinephrine toxicity, and seminal vesicle contraction indicate that buspirone lacks direct interaction at these sites [Riblet et al., 1982; Allen et al., 1974]. However, buspirone increases locus coeruleus noradrenergic neuronal activity and norepinephrine metabolism [Sanghera et al., 1983; Hjorth and Carlsson, 1982]. This action is in direct opposition to effects seen with benzodiazepines. Such indirect actions on numerous brain systems (including dopamine, see below) have led to the concept that buspirone may act as a "midbrain modulator" [Eison and Eison, 1983, this volume].

It therefore appears that buspirone and the benzodiazepines share little in terms of action, with the exception of the end result—the reduction of anxiety in the clinic. It is certainly well accepted that buspirone has an effect on the dopaminergic system, and it has been proposed that this interaction may be responsible for the drug's anxiolytic effect [Stanton et al., 1981] and, in fact, for that of the benzodiazepines as well [Taylor et al., 1982].

Dopaminergic Interactions

The profile of buspirone's interaction with the dopaminergic systems of the brain deserves historic review. Allen et al. [1974] noted that buspirone prevents apomorphine-induced emesis in dogs and blocks the conditioned avoidance response. Further, it elevates striatal levels of 3,4-dihydroxyphenylacetic acid (DOPAC), 3,4-dihydroxyphenylalanine (DOPA), and homovanillic acid (HVA) and inhibits apomorphine-induced stereotypy in rats [Stanley et al., 1979; Riblet et al., 1982; McMillen and Mattiace, 1983a; McMillen et al., 1983; Cimino et al., 1983; McMillen and McDonald, 1983; Hjorth and Carlsson, 1982; Hyslop et al., 1982; Wood et al., 1983]. Buspirone decreases striatal acetylcholine levels [Kolasa et al., 1982]. Buspirone at high doses (30 mg) elevates prolactin levels in man, although at clinically relevant doses, no consistent effects on prolactin levels were seen with either buspirone or diazepam [Meltzer and Fleming, 1982; Lader, 1982]. Thus, buspirone antagonizes presumably dopamine-mediated behaviors. However, it is known that the conditioned avoidance response is blocked by benzodiazepines (see above), agents which lack direct dopaminergic action. Under dosing conditions relevant to conflict activity, buspirone's effect on DOPA levels resembles that of apomorphine, the dopamine agonist, rather than the antagonist trifluoperazine (see Table 2). Moreover, anticholinergic and antihistaminic drugs such as scopolamine and diphenhydramine can prevent emesis without postsynaptic dopamine receptor blockade. Furthermore, picrotoxin reduces striatal levels of acetylcholine [Scatton and Bartholini, 1980]. Finally, the release of prolactin is a complexly regulated event, being also controlled by opiate, histaminergic, and GABAergic pathways, for example [Grandison, 1981].

While the actions of buspirone mentioned above appear to be consistent with postsynaptic dopamine receptor blockade, there are a number of laboratory findings which argue against such a determination. Behaviorally, buspirone can mimic, and certainly not inhibit, apomorphine's (presumably postsynaptic) ability to induce contralateral rotation in rats which have been unilaterally lesioned in the substantia nigra [Riblet et al., 1982; McMillen et al., 1983]. The quantitative electroencephalogram of buspirone resembles those of piribedil (a dopamine agonist) and apomorphine. The characteristic envelopes of power spectral observations for these compounds is in marked contrast to that obtained for dopamine antagonists such as thioridazine [Riblet et al., 1982]. Buspirone, like dopamine and apomorphine, inhibits the electrogenically induced elevation of perfusion pressure in the isolated rabbit ear artery in a fashion which can be reversed by dopamine antagonists [Riblet et al., 1982]. Unlike conventional antipsychotics, buspirone does not elevate striatal levels of 3-methoxytyramine, the metabolite produced from synaptically released dopamine [Cimino et al., 1983]. Like diazepam and in contrast to antipsychotics, buspirone elevates growth hormone levels in humans [Meltzer and Fleming, 1982]. In rats pretreatment with reserpine blunts the effect of buspirone, but not that of haloperidol, on prolactin levels [Meltzer and Fleming, 1982]. Buspirone administration

TABLE 2. Effect of Anxiolytic Agents on Striatal Levels of DOPA*

Time after treatment (min)	Percent change from control			
	Trifluoperazine (0.25, p.o.)[a]	Buspirone (4, p.o.)[a]	Apomorphine (0.01, s.c.)[a]	Piribedil (10, s.c.)[a]
10	63 ± 11	143 ± 17	143 ± 5	91 ± 9
20	62 ± 11	208 ± 50	116 ± 10	131 ± 39
30	70 ± 9	119 ± 23	117 ± 11	110 ± 8
40	68 ± 8	134 ± 17	123 ± 8	122 ± 14

*Male Sprague-Dawley rats received drugs at two times the minimally effective dose for attenuation of punishment-suppressed responding [Taylor et al., 1983]. At the indicated time, animals received 750 mg/kg, i.p., γ-butyrolactone followed 5 min later by 100 mg/kg, i.p., *m*-hydroxybenzylhydrazine. Thirty min later the animals were sacrificed and the striata dissected and frozen. DOPA was extracted in 0.1 M perchloric acid, as described by Arneric et al. [1981] and separated from other components by high pressure liquid chromatography using an Ultrasphere® C_{18} 5 μm column. The mobile phase consisted of 100 mM monosodium phosphate, 1 mM disodium edetate, and 0.0025 % 1-octanesulfonic acid, sodium salt monohydrate, pH 3.0 (20°C). Detection was accomplished with the use of Bioanalytical Systems LC-4 amperometric detector employing a glassy carbon electrode set at a potential difference of +0.07V. Results are shown as percent of "zero time" animals which received γ-butyrolactone and *m*-hydroxybenzylhydrazine only on that day. Each anxiolytic agent was tested on a separate day; the control group and the data for each time point were obtained from ten animals per group. The "zero time" values, in pmol DOPA/mg protein, for each respective drug were as follows: trifluoperazine, 246 ± 44; buspirone, 240 ± 36; apomorphine, 257 ± 30; piribedil, 132 ± 11.
[a]Dose, mg/kg, route.

does not produce catalepsy, a further distinction from conventional antipsychotics and a persuasive argument that the clinical use of this drug will not be tainted by the occurrence of extrapyramidal side effects [Riblet et al., 1982; McMillen et al., 1983; Gershon and Eison, 1983]. Unlike the so-called "atypical" antipsychotics, clozapine, sulpiride, and molindone, buspirone actually *reverses* the catalepsy induced by postsynaptic dopamine antagonists, such as trifluoperazine, haloperidol, and *cis*-flupenthixol, in a fashion that resembles apomorphine and piribedil [Riblet et al., 1982; McMillen and McDonald; 1983]. This reversal appears to be independent of presynaptic dopamine release because the phenomenon is even observed following treatment with the dopamine-depleting agent Ro4-1284 [McMillen and McDonald, 1983]. In fact, this unique property of buspirone has led to the proposal that this drug may be of value in idiosyncratic or neuroleptic-induced parkinsonism [McMillen and McDonald, 1983]. Therefore, it can no longer be concluded that buspirone's prevention of apomorphine-induced behaviors resides in its ability to block postsynaptic dopamine receptors in a fashion qualitatively resembling the current antipsychotic drugs, including clozapine.

In vitro observations of dopamine receptor binding are consistent with the distinction of buspirone from clozapine, sulpiride, and thioridazine, and its resemblance to dopamine, apomorphine, N-n-propylnorapomorphine, and piribedil. The dopamine antagonists inhibit [^{3}H]spiperone binding to rat striatal membranes equally well in the presence or absence of guanyl nucleotides. In contrast, buspirone and the dopamine agonists become less potent inhibitors of [^{3}H]spiperone binding in the presence of guanyl nucleotides [Riblet et al., 1982]. A further difference between buspirone and the postsynaptic dopamine antagonists may be discerned following chronic treatment. When anxiolytically relevant doses (two times the minimally effective dose for attenuation of punishment-suppressed responding [Taylor et al., 1982; Hyslop et al., 1982]) were administered three times a day for 29 days to male Sprague-Dawley rats, buspirone did not alter [^{3}H]spiperone binding in vitro to striatal membranes, whereas trifluoperazine produced an increase in binding (see Table 3). Similar findings were obtained comparing buspirone (3 mg/kg/day) with trifluoperazine (1 mg/kg/day) for longer

TABLE 3. The Effect of Chronic Drug Treatment on [^{3}H]Spiperone Binding to Rat Striatal Membranes In Vitro†

Treatment (dose, mg/kg, p.o.)	[^{3}H]Spiperone bound (mean fmol/mg protein ± SEM, n)
Vehicle	16.2 ± 1.9 (14)
Buspirone (2)	14.8 ± 1.3 (13)
Trifluoperazine (0.5)	21.3 ± 1.6 (12)*

†Male Sprague-Dawley rats received vehicle or drug at the doses shown three times a day for 29 days. Twenty-four hours later, animals were sacrificed and striata were dissected and frozen. Binding of [^{3}H]spiperone was assayed according to the method of Burt et al. [1976], using a single radioligand concentration of 80 pM (K_D was 180 pM for control animals).
*$P < 0.05$ vs. vehicle and buspirone-treated animals (Student's t-test, two-tailed).

time periods (90 days [McMillen, 1983]). In an even more rigorous trial, chronic administration of a high dose of buspirone (20 mg/kg, p.o., twice daily) for 25 days had no effect on [^{3}H]spiperone equilibrium binding characteristics [Cimino et al., 1983]. Dopamine receptor supersensitivity has been noted following chronic administration with neuroleptics, and it has been postulated that preclinical studies such as these serve as predictors of the incidence of tardive dyskinesias following clinical use [Burt et al., 1977]. Taken together, these data strongly suggest that clinical use of buspirone should not lead to tardive dyskinesia. Indeed, the ability of buspirone to reverse trifluoperazine-induced catalepsy in rats led McMillen [1983] to determine what effect buspirone would have on animals receiving chronic neuroleptic treatment. Co-administration of buspirone (1 mg/kg/day, via osmotic minipumps) for the last 2 wk of trifluoperazine treatment (1 mg/kg/day, p.o., for 90 days) significantly reversed the increase in [^{3}H]spiperone binding in vitro to dopamine receptor binding sites on striatal membranes following treatment with trifluoperazine alone. This exciting and provocative result suggests that buspirone will not cause tardive dyskinesia, but in fact, its coadministration will block or even reverse that resulting from concurrent antipsychotic pharmacotherapy.

In summary, the extension and elaboration of buspirone's pharmacology have altered the impression that buspirone was a typical postsynaptic dopamine antagonist resembling conventional antipsychotic drugs. This expansion in our body of knowledge has largely occurred in the areas of behavior, neurochemistry, and molecular pharmacology; the most promising and exciting studies, employing electrophysiological and anatomical techniques, are just beginning.

BUSPIRONE'S MECHANISM OF ACTION

How, then, does buspirone accomplish its anxiolytic action? The answer to this question perhaps lies at the core of our understanding the neural substrates of anxiety. McMillen et al. [1983] have supplied data which suggest that buspirone acts as a *pre*synaptic dopamine antagonist, possibly enhancing dopamine impulse flow to mesolimbic or mesocortical regions. It may well be that buspirone's dopaminergic actions are not related to the relief of anxiety as recently theorized [Taylor et al., 1982, 1983]. For instance, the *gem*-dimethylglutarimide analog of buspirone, MJ 13805, possesses potent anxiolytic activity in animal models (equivalent to buspirone) yet is effectively devoid of affinity for dopamine sites labeled by [^{3}H]spiperone *in vitro* [Eison et al., 1982; McMillen and Mattiace, 1983a,b; Temple et al., 1982]. Similarly, buspirone's metabolite, 1-(2-pyrimidinyl)piperazine, possesses anxioselective properties without dopaminergic effects [Eison, personal communication]. Buspirone possesses

subtle interactions with the serotonergic and noradrenergic systems which have been implicated in anxiety. Although a direct interaction with the benzodiazepine-GABA system appears to be excluded, buspirone is perhaps not silent here [see Eison and Eison, 1983, this volume]. Anxiety is undoubtedly a multidimensional disorder of the central nervous system. Therefore, to be anxioselective, a drug may (paradoxically) be required to have multifaceted actions. The recognition that buspirone has such actions has led to the conception that it represents the first of a new class of psychotropic agents, the "midbrain modulators" [Eison and Eison, 1983, this volume]. Williams [1983] has suggested that benzodiazepines are second-generation psychotropic agents because they facilitate a single neurotransmitter, GABA, rather than accomplishing selective agonism or antagonism at such a site themselves. By extension, a "midbrain modulator" like buspirone would represent the third generation of psychotropic agents by facilitating the action of endogenous factors in a complex fashion.

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