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Pharmacological and Clinical Effects of Buspirone

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TAYLOR, D. P., M. S. EISON, L. A. RIBLET AND C. P. VANDERMAELEN. *Pharmacological and clinical effects of buspirone.* PHARMACOL BIOCHEM BEHAV **23**(4) 687–694, 1985.—Clinical trials have demonstrated that buspirone (BuSpar®) is effective in the treatment of anxiety with efficacy and dosage comparable to diazepam or chlorazepate. Buspirone has a unique structure and a pharmacologic profile which distinguishes it from the benzodiazepines. Because it lacks the anticonvulsant, sedative, and muscle-relaxant properties associated with other anxiolytics, buspirone has been termed "anxioselective." Animal studies suggest that it lacks potential for abuse, and this finding is supported by clinical investigations. Further preclinical work supports the contention that buspirone lacks liability to produce physical dependence or to significantly interact with central nervous system depressants such as ethanol. Moreover, biochemical investigations have not identified any direct interaction of buspirone with the benzodiazepine-γ-aminobutyric acid-chloride ionophore complex. Pharmacologic studies on the molecular level indicate that buspirone interacts with dopamine and serotonin receptors. Recent behavioral, electrophysiological, and biochemical studies have clearly demonstrated that early hypotheses that buspirone might be considered a neuroleptic are no longer tenable. Recent evidence indicates that other neurotransmitter systems (serotonin, norepinephrine, acetylcholine) mediate buspirone's effects. It is hoped that future studies can define the mechanism by which buspirone alleviates the clinical manifestations of anxiety.

Buspirone Nonbenzodiazepine Anxiety Anxiolytic Antianxiety agent Anxioselective BuSpar®

FEW would dispute that general anxiety disorder is a crippling and disabling emotional disorder. Antianxiety agents, especially the benzodiazepines, have been widely prescribed because of their success in ameliorating the symptoms of this disorder. The benzodiazepines are also noted for a profile of action which includes sedative, anticonvulsant, and muscle relaxant properties. This prototypical class of antianxiety drugs also possess certain undesirable properties, including often lethal interactions with alcohol or other central nervous system depressants, and a propensity to induce physical dependence after long-term use. The continuing search for agents which act more exclusively against anxiety and have fewer side effects has led to the discovery and evaluation of a new class of nonbenzodiazepine compounds. A prototype for this new class is buspirone (BuSpar®). It is the purpose of this paper to discuss the differences between buspirone and the benzodiazepines with respect to chemical structure, pharmacology, anxioselective clinical profile, and mechanism of action.

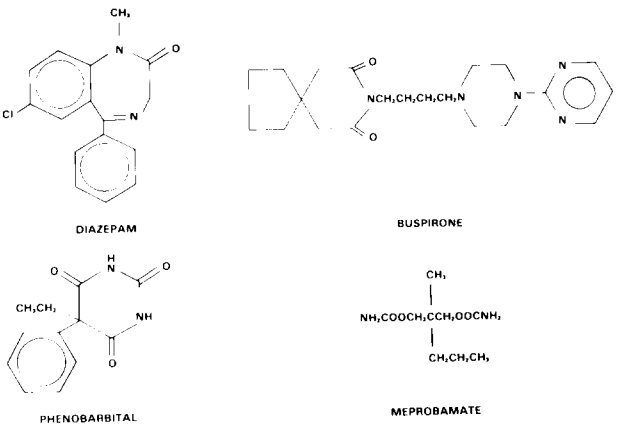

FIG. 1. Structures of drugs from representative classes which have been used in the relief of anxiety.

CHEMICAL STRUCTURE

In Fig. 1, it can be seen that buspirone does not share the benzodiazepine nucleus, nor is it similar to historic anxiolytic agents such as the barbiturates, or the propanediol carbamates, such as meprobamate. Buspirone may be referred to as an azaspirodecanedione [43].

PHARMACOLOGY

Like the benzodiazepines and other anxiolytic compounds, buspirone is active in the Vogel conflict paradigm (see Table 1). The potency of buspirone in this paradigm is comparable to the benzodiazepines (see Table 2) [36]. Buspirone has also been reported to be active in the Vogel

TABLE 1

ACTIVITY OF ANXIOLYTICS IN THE VOGEL CONFLICT MODEL

Dose (mg/kg, PO)	Mean Total Licks (Percent of Control) Buspirone	Diazepam
0	100	100
0.05	—	114
0.1	—	91
0.5	78	209*
1.0	270*	144
5.0	393*	208*
8.0	182*	—
10.0	337*	—

Activity was determined by a modification of the drinking conflict paradigm of Vogel *et al.* [40]. Control animals treated with appropriate vehicle took 48 licks (water; buspirone) or 25 licks (0.2 percent methyl cellulose in water; diazepam).

*$p<0.05$ vs. respective vehicle (Multiple t-test).

TABLE 2

ANTICONFLICT ACTIVITY OF VARIOUS DRUGS

Drug	Minimally Effective Dose (mg/kg, PO)
Diazepam	0.5
Chlordiazepoxide	0.5
Buspirone	1.0
Bromocriptine	10.0

TABLE 3

ANTICONVULSANT ACTIVITY OF ANXIOLYTICS

Convulsant Agent		ED_{50} (mg/kg, PO) Diazepam	Buspirone
Bicuculline	—Rat	79	>400*
Pentylenetetrazol	—Rat	2.5	>400*
Picrotoxin	—Rat	110	>400*
Strychnine	—Rat	>400*	>400*
	—Mouse	6.6	>400*
Maximal electroshock	—Mouse	18	370

*No protection observed at this dose.

TABLE 4

MUSCLE RELAXANT PROPERTIES OF ANXIOLYTICS

Species	ED_{50} (mg/kg, PO) Diazepam	Buspirone
Mouse	1.6	180
Rat	14	>400

TABLE 5

LOSS OF RIGHTING REFLEX: INTERACTION OF ANXIOLYTICS WITH CNS DEPRESSANTS

CNS Depressant	ED_{50} (mg/kg, PO) Diazepam	Clorazepate	Buspirone
Hexobarbital			
—Mouse	0.35	0.69	55
—Rat	0.2	2.3	16
Ethanol			
—Mouse	1.0	0.57	63
—Rat	1.1	2.5	47

TABLE 6

ACTIVITY OF BUSPIRONE IN MODELS OF ABUSE POTENTIAL AND LIABILITY FOR PHYSICAL DEPENDENCE

Method	Response
Self-administration in the monkey	Inactive
Drug discrimination in the rat	Inactive
Signs of withdrawal after chronic administration	Inactive
Ability to substitute for barbiturate after chronic administration	Inactive

TABLE 7

EFFICACY OF ANXIOLYTICS IN A PRELIMINARY CONTROLLED STUDY

Treatment:	Placebo	Diazepam	Buspirone
Number of Patients	18	20	18
Mean Daily Dose (mg)		18.7	19.6
Final Score, Hamilton Anxiety Rating Scale	21.6	10.6*	6.6*
Side Effects (Reports/Visits)	12/72	14/80	5/72

Data from Goldberg and Finnerty [10].

*$p<0.01$ vs. placebo.

paradigm in other laboratories ([2, 25, 41] Tenen, personal communication), as well as in the original Geller-Seifter conflict model [14].

However, unlike the benzodiazepines, buspirone is not active in the prevention or reversal of chemically or electrically-induced convulsions (see Table 3) [26]; nor does buspirone share the muscle relaxation properties of the benzodiazepines as evidenced by its relative lack of potency to induce muscle weakness in the hanging bar test (see Table 4) [26]. Buspirone, unlike the benzodiazepines, does not significantly potentiate the hypnotic effects of hexobarbital or ethanol in either the mouse or the rat (see Table 5) [26].

The ability of buspirone to induce physical dependence has been tested in at least two different paradigms. In one of these, buspirone and benzodiazepines were chronically ad-

TABLE 8
EFFICACY OF ANXIOLYTICS IN A CONTROLLED STUDY

Treatment	Placebo	Diazepam	Buspirone
Number of Patients	73	71	68
Mean Daily Dose (mg)	—	20	20
Final Psychiatric Rating Scores			
Hamilton Anxiety Scale	21	13*	15*
Global Anxiety Assessment	4.6	3.6*	3.7*
Hopkins Symptom Check List	104	96*	95*
Profile of Moods Scale	168	156*	150*
Side Effects			
Sleepiness (percent)	12	32*	20
Fatigue (percent)	0	20*	2

Data from Rickels *et al.* [27].
*$p<0.05$ vs. placebo.

TABLE 9
PERFORMANCE IMPAIRMENT BY ANXIOLYTICS: DRIVING SIMULATOR

Treatment	Placebo	Diazepam	Buspirone
Dose (mg)	—	15	20
Worst Performance			
Day 1	4	15*	1
Day 8	2	18*	0
Day 9†	4	15*	1
Best Performance			
Day 1	6	0.5*	13.5
Day 8	5.5	0*	14.5
Day 9†	7	2*	11.0

Data are from Moskowitz and Smiley [24].
*$p<0.05$ vs. placebo.
†On Day 9 all subjects received ethanol to 0.10 percent blood alcohol content.

TABLE 10
DIVIDED ATTENTION TASK RESULTS: COMBINED ERRORS

Treatment	Placebo	Diazepam	Buspirone
Day 1			
1 Hour post-dose	4.26	6.67	3.35
Day 8			
Pre-dose	3.43	3.51	3.04
1 Hour post-dose	5.53	7.71	2.42*
Day 9†			
1 Hour post-dose	10.47	14.34	4.23‡

Data are from Moskowitz and Smiley [24].
*$p<0.05$, buspirone vs. diazepam.
†On Day 9 all subjects received ethanol to 0.10 percent blood alcohol content.
‡$p<0.05$, buspirone vs. placebo.

TABLE 11
ABUSE POTENTIAL OF ANXIOLYTICS ASSESSED BY SEDATIVE ABUSERS

Drug, Dose	Liking Score*	Street Value
Methaqualone, 300 mg	13.5	$3.50
Diazepam, 20 mg	10.6	$1.94
10 mg	6.3	$0.68
Buspirone, 10 mg	4.2	$0.24
40 mg	3.6	$0.56
Placebo	3.2	$0.23

Data are from Cole *et al.* [5].
*16=Extreme like, 0=Extreme dislike, 8=neither like nor dislike.

ministered at 200 mg/kg per day to rats. After 21 days of treatment, the drug was withdrawn and changes in body weight were determined. In the case of diazepam, as had been seen previously with dependence-producing drugs such as morphine and barbiturates, body weight dropped on two days of withdrawal. When drug treatment was reinstituted 2 days later, changes in body weight resumed their normal climb. In contrast, cessation of buspirone treatment led to an increase in body weight, which returned to the base line rate of gain when drug treatment was reinstituted [32]. Secondly, chronic treatment with barbiturates followed by withdrawal can lead to convulsions. Benzodiazepines, such as diazepam, block these withdrawal-induced convulsions, whereas buspirone is inactive [26].

Buspirone's potential for abuse has been assessed in two

TABLE 12
PRECLINICAL PROPERTIES OF SEVERAL DRUG CLASSES

Property	Benzodiazepine	Buspirone	Neuroleptics
Inhibition of conditioned avoidance response	Active	Active	Active
Inhibition of apomorphine-induced stereotypy	Inactive	Active	Active
Inhibition of apomorphine-induced rotation	Inactive	Inactive	Active
Induction of catalepsy	Inactive	Inactive	Active
Reversal of neuroleptic-induced catalepsy	Inactive	Active	Inactive
Effects on neuronal activity			
Substantia nigra	Decrease	Potent enhancement	Enhancement
Locus coeruleus	Decrease	Enhancement	
Dorsal raphe nucleus	Decrease	Decrease	Variable
Benzodiazepine binding			
In vitro	Inhibit	Inactive	Inactive
In vivo	Inhibit	Enhance	
Dopamine binding	Inactive	Inhibit	Inhibit
GTP shift present?		Yes	No
Effects of chronic treatment			
Induces supersensitivity?	No	No	Yes
Reverse neuroleptic-induced supersensitivity?	No	Yes	No
Inhibit tyrosine hydroxylase?		Yes	Yes
Inhibit dopamine-stimulated adenylate cyclase?		Weakly	Potently
Effects on neurotransmitter and metabolite levels			
DOPAC	Decrease	Increase	Increase
HVA	Decrease	Increase	Increase
ACh	Increase	Decrease	Decrease
3-MT	No effect	No effect	Increase
5-HIAA	Decrease	Decrease	
MHPG	Decrease	Increase	

different systems. In self-administration studies, monkeys were trained to deliver intravenous cocaine, and then given various drugs in a substitution paradigm. Under these conditions, buspirone did not reinforce self-administration, but rather was treated as saline [1]. In another test of abuse potential, rats were trained to discriminate pentobarbital from saline, or oxazepam from saline or buspirone from saline. Animals trained to recognize either pentobarbital or oxazepam generalized to the other drug. Unlike these agents, buspirone did not serve as a robustly-recognized cue. Secondly, neither pentobarbital nor oxazepam generalized to buspirone in buspirone-trained animals [15] (see Table 6).

Thus, the preclinical pharmacology of buspirone supports the prediction of an "anxioselective" clinical profile of action [35], defined as the relief of anxiety in the absence of muscle relaxation, seizure control, significant interaction with central nervous system depressants, physical dependence and the propensity to promote abuse.

ANXIOSELECTIVE CLINICAL PROFILE

The preclinical prediction of an anxioselective profile for buspirone is corroborated by clinical data. Buspirone has been shown to be as effective as diazepam in the treatment of anxiety (generalized anxiety disorder) in several clinical trials. For instance, in the pioneering work of Goldberg and Finnerty [10], buspirone and diazepam were approximately equipotent in the treatment of generalized anxiety disorder (see Table 7). Despite significant decreases in Hamilton anxiety scores following four weeks' administration, buspirone produced significantly fewer side effects than diazepam as reflected by reports per visit. In a second study, Rickels and co-workers [27] showed buspirone to be equivalent on a milligram basis with diazepam, with both drugs inducing a significant decrease in Hamilton anxiety scores relative to placebo (see Table 8). Significant decreases in anxiety were also obtained using global assessment, the Hopkins Symptom Check List, and the Profile of Moods Scale. It is significant that buspirone produced less sleepiness and fatigue than diazepam in this trial. Similar results have been reported in other recently published studies [7, 11, 29, 42].

Buspirone induced less psychomotor impairment than the benzodiazepines. For example, in studies by Moskowitz and Smiley [24], subjects received buspirone, diazepam or placebo for eight days. On the first day, performance on twenty different variables in a driving simulation task was

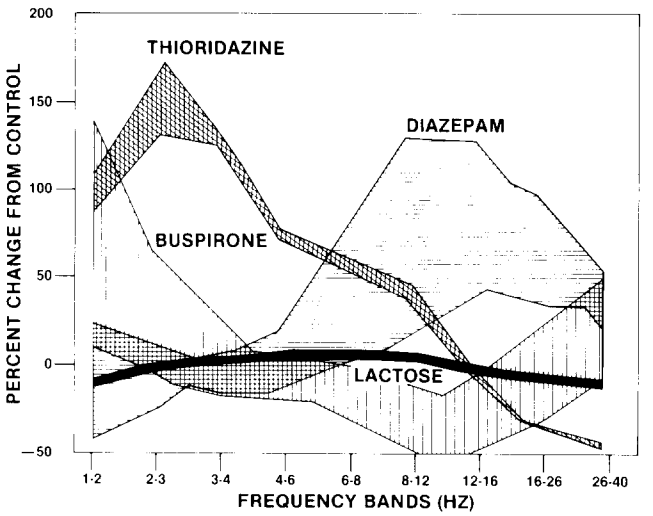

FIG. 2. Zero-cross EEG analysis of psychotropic agents. Groups of six cats were monitored before and after receiving drugs. Changes in integrated power from cortical electrodes were calculated as percent difference from pre-drug spectra for each band width. Data represent "envelopes" generated by a variety of doses of each drug. Drugs employed were lactose (black line), buspirone, 0.3–20 mg/kg, PO (vertical lines), diazepam, 0.3–5.0 mg/kg, PO (horizontal lines), and thioridazine, 2.5–5.0 mg/kg PO (cross-hatched area).

TABLE 13

BUSPIRONE X DIAZEPAM INTERACTIONS: HORIZONTAL BAR TEST IN RATS

Pretreatment (mg/kg, PO)	Induction of Muscle Weakness by Diazepam, ED_{50} (mg/kg, PO)*
Water	13.6 (8.1–22.8)
Buspirone (5)	15.2 (10.5–22.0)
(20)	13.6 (8.1–22.8)

Ten minutes after pretreatment animals received diazepam. The induction of muscle weakness was assessed one hour later.
*95 percent fiducial limits given in parentheses.

TABLE 14

BUSPIRONE X DIAZEPAM INTERACTIONS: LOSS OF RIGHTING REFLEX IN RATS

Pretreatment (mg/kg, PO)	Induction of Hypnosis, ED_{50} (mg/kg, PO)* By Diazepam	By Chloral Hydrate
Water	508.6 (266.3–971.3)	148.9 (112.5–196.9)
Buspirone (5)	473.8 (312.0–719.4)	140.5 (99.5–198.4)
(20)	435.7 (270.3–702.3)	148.9 (112.5–196.9)

Ten minutes after pretreatment animals received hypnotics. Loss of righting reflex was assessed over the two subsequent hours.
*95 percent fiducial limits given in parentheses.

assessed. Subjects receiving diazepam were the worst drivers on fifteen of the different parameters (see Table 9). Subjects receiving buspirone performed better than diazepam or placebo-treated subjects on thirteen of the different parameters. These differences were statistically significant. By day eight, the worst drivers continued to be diazepam-treated subjects who showed no toleration to diazepam-induced performance impairment. Similarly, buspirone-treated drivers continued to be the best on fourteen of the driving parameters. These differences were again significant. On the ninth day, in addition to drug or placebo, subjects received sufficient alcohol to achieve blood alcohol levels of 0.1 percent. Diazepam-treated drivers performed most poorly in the presence of alcohol on fifteen of the different parameters. In contrast, buspirone-treated drivers were the best performers on eleven driving skills measures. Again, these differences were significant. It is notable that buspirone actually enhanced performance relative to placebo in some areas, such as the combined number of errors on divided attention tasks, especially in the presence of alcohol (see Table 10). These data illustrate that after eight days of treatment the detrimental effects of the benzodiazepine upon performance had not "tolerated out." Similar work has been reported Matilla and co-workers [19].

The potential for recreational abuse of buspirone by sedative abusers was assessed in the laboratory of Cole and his colleagues [5]. In this laboratory, recreational sedative abusers were given doses of various drugs and asked to indicate, on a sixteen centimeter linear scale, their impression of the drug recently taken. A score of zero would reflect extreme dislike (i.e., never wish to take this drug again) while a score of sixteen would reflect an extremely favorable impression (i.e., the subject would definitely enjoy taking this drug again). A 300 mg dose of methaqualone produced a liking score of 13.5 (see Table 11). A dose of diazepam 20 mg produced a liking score of 10.6, while 10 mg produced a neutral score. Like placebo, buspirone at either 10 or 40 mg produced liking scores between 3 and 4. A second means of assessing abuse potential was the assignment of a street value by this same group for the drugs in question. The approximate street value for methaqualone was $3.50; for diazepam, $1.94 at 20 mg and $0.68 at 10 mg. Buspirone at 40 mg was assessed at $0.56, and at 10 mg was roughly the same as placebo, $0.24 and $0.23, respectively.

MECHANISM OF ACTION

Can the anxioselective clinical profile of buspirone be associated with a mechanism of action that significantly differs from that of the benzodiazepines? The behavioral, electrophysiological, and biochemical effects of buspirone in a wide variety of preclinical tests have recently been reviewed [6,32]. These studies have served to distinguish buspirone from both the benzodiazepines and the neuroleptics (see Table 12). A comprehensive review of these investigations is beyond the scope of this paper; however, a few examples from the various fields of investigation will serve to highlight the similarities and distinctions between buspirone and these other classes of psychotropic drugs.

Like the benzodiazepines, buspirone inhibits conditioned avoidance responding [30,31]. However, the quantity of buspirone required to produce this effect exceeds anxiolytically-relevant doses. Buspirone is effective in the blockade of apomorphine-induced stereotypy, whereas the

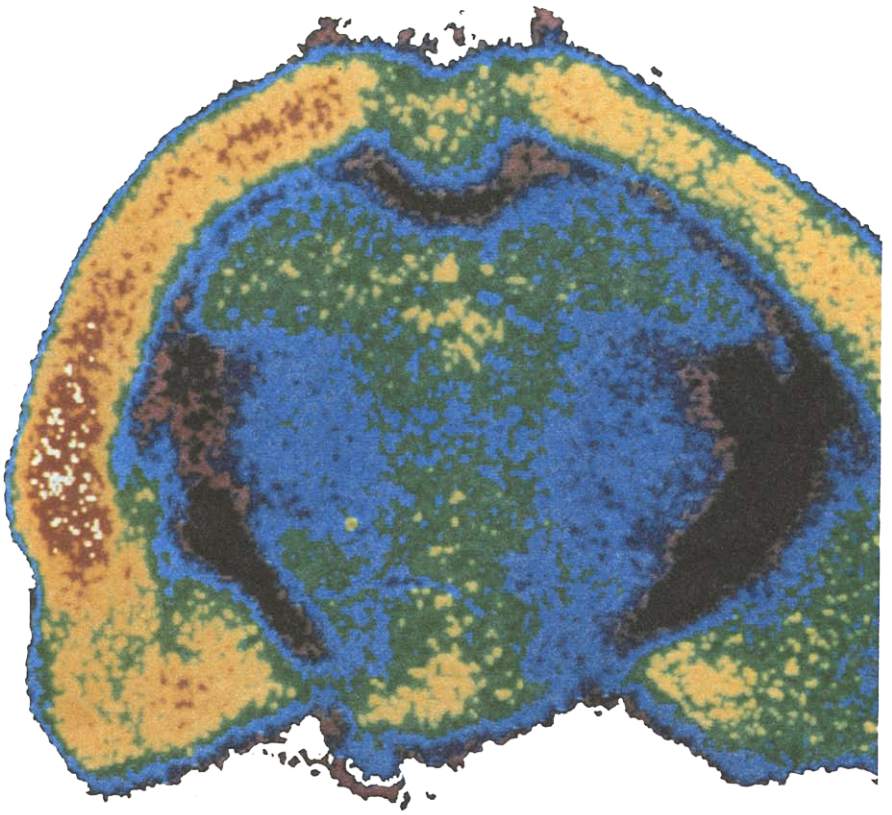

FIG. 3. Pseudo-color image of an autoradiogram of rat brain reflecting total binding of [^{3}H]buspirone. Intensely-labeled areas are red, while more sparsely-labeled regions progress through the spectrum to violet.

benzodiazepines are not [31]. Although this property is shared with antipsychotic agents, it is notable that buspirone does not block apomorphine-induced rotation, whereas the antipsychotics do [22]. Furthermore, antipsychotics (with the exception of clozapine) induce catalepsy, whereas buspirone not only fails to induce catalepsy, but in fact reverses catalepsy previously induced by a variety of antipsychotic treatments [23,26].

Benzodiazepines have been reported to inhibit the neuronal activity of dopaminergic neurons in the substantia nigra [18]. Antipsychotic agents, on the other hand, have been noted for their enhancement of firing in this region of the brain; however, maximal elevation observed with haloperidol is approximately 20 percent. Buspirone also enhances firing in this region, but its maximal effect approaches a 100 percent increase [22]. In the locus coeruleus, buspirone moderately increases firing of noradrenergic neurons [28]. In this region, benzodiazepines inhibit firing [12,18]. Recently it has been shown that buspirone potently inhibits the firing of cells in the dorsal raphe nucleus [38,39]. This occurs with either systemic or iontophoretic application of the drug. Furthermore, the application of buspirone to perfusion media in brain slice preparations containing the dorsal raphe nucleus indicates that this effect of buspirone is direct, not mediated by a polysynaptic event nor by a metabolite of buspirone. The benzodiazepines, in higher doses than buspirone, also inhibit the firing of serotonergic dorsal raphe neurons, at least in unanesthetized animals [18,37]. The neuroleptics vary in their effects in this test system [8]. Finally, buspirone has an electroencephalographic profile which is unique and distinct from both the antipsychotics and the benzodiazepines (see Fig. 2) [26].

Buspirone presents a profile in various molecular pharmacologic assays which is distinct from the benzodiazepines and other psychotropic drugs. For instance, buspirone has no effect on *in vitro* benzodiazepine binding, whereas *in vivo* it enhances benzodiazepine binding; this contrasts with the benzodiazepines themselves which inhibit binding [9, 25, 32, 34, 41]. Like antipsychotics, buspirone inhibits acute dopamine binding *in vitro* [31]. However, in the presence of guanosine triphosphate, buspirone exhibits an agonist-like shift. It is well known that after chronic administration, antipsychotics produce supersensitivity which is seen as an increase in the number of dopamine receptors in *in vitro* binding assays [3]. Like the benzodiazepines, buspirone does not produce this effect [4, 17, 20, 32]. Moreover, buspirone, when

administered concurrently with antipsychotics, will prevent the increase in receptor number seen with antipsychotics alone [20,21]. Although buspirone and antipsychotics inhibit tyrosine hydroxylase activity, buspirone exhibits only marginal potency in the inhibition of dopamine-stimulated adenylate cyclase [4,23]. Buspirone is further distinguished from the antipsychotics and benzodiazepines by its effects on neurotransmitters and their metabolites in various brain regions. For example, benzodiazepines decrease the levels of dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the striatum while increasing the levels of acetylcholine (ACh). In contrast, buspirone increases DOPAC and HVA and decreases ACh levels [4,22]. While the neuroleptics share these effects of buspirone, they also increase the levels of 3-methoxytyramine (3-MT) in the striatum, an effect which is not observed with buspirone [4]. Buspirone shares with the benzodiazepines the ability to decrease levels of 5-hydroxyindoleacetic acid (5-HIAA) in the hippocampus, but unlike the benzodiazepines, it increases rather than decreases levels of 3-methoxy-4-hydroxyl-phenyl glycol (MHPG) [4,16].

As mentioned above, *in vivo* binding studies with [^{3}H]diazepam reveal that buspirone can enhance the binding of diazepam in some brain regions. This biochemical data has behavioral relevance in that buspirone can interact with diazepam. For instance, pretreatment with buspirone enhances the Vogel anticonflict activity of a fixed dose of diazepam in a dose-dependent fashion [6]. However, buspirone pretreatment does not alter diazepam's induction of muscle weakness or loss of righting reflex (see Tables 13 and 14). We have recently obtained *in vivo* autoradiographic localization of radioactivity originating from [^{3}H]buspirone. This distribution reveals local concentrations of radioactivity in parietal cortex and amygdala which are distinct from the distribution seen with [^{3}H]diazepam (see Fig. 3) [33].

In view of the unique and complex preclinical profile of buspirone, one must ask the question as to how buspirone accomplishes its anxiolytic action. Buspirone influences a variety of neurotransmitter systems in a variety of brain regions. The ability to produce these changes simultaneously has led to the recent working hypothesis that buspirone may act as a "midbrain modulator" [6]. This concept functions as a useful heuristic description of the properties of buspirone which distinguish it from other psychotropic drug classes; however, the precise mechanism by which buspirone alleviates the clinical manifestations of anxiety continues to be undefined. Buspirone's effects on neuronal firing in the dorsal raphe nucleus are consistent with some contemporary views of anxiolysis [13], while its effects in the locus coeruleus may account for its ability to reduce anxiety in the presence of a fully alert state.

CONCLUSION

In summary, buspirone exhibits a significant number of pharmacological differences from benzodiazepines. It lacks anticonvulsive properties, it has minimal sedative activity, buspirone minimally interacts with depressants, it lacks muscle relaxation, and exhibits no potential to impair performance. In contrast to the benzodiazepines, buspirone does not produce physical dependence and lacks abuse potential. Buspirone does not alter *in vitro* benzodiazepine or GABA binding, although it enhances *in vivo* benzodiazepine binding. Buspirone does not antagonize stress-induced increases in cortical dopamine turnover and decreases rather than increases acetylcholine levels. Buspirone increases rather than decreases locus coeruleus noradrenergic neuronal firing and inhibits dorsal raphe serotonergic firing. Buspirone differs from the benzodiazepines in its chemical structure, its pharmacology, its anxioselective profile and its mechanism of action.

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