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DOPAMINE RECEPTOR ANTAGONISM BY THE NOVEL ANTI-ANXIETY DRUG, BUSPIRONE[1]

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Abstract

Buspirone is an anxiolytic drug with a clinical potency similar to that of diazepam, but it lacks affinity for diazepam of γ-aminobutyric acid (GABA) binding sites. Because previous reports suggested that buspirone may possess dopamine (DA) agonist activity, buspirone was tested for effects on DA neurotransmission. At presynaptic DA receptors, unlike other DA agonists, buspirone inhibited neither synaptosomal tyrosine hydroxylase activity nor the *in vivo* γ-butyrolactone-induced activation of striatal tyrosine hydroxylase. However, buspirone did inhibit the action of apomorphine, a direct acting DA agonist, in both of these DA autoreceptor test systems with a potency similar to that of chlorpromazine. Striatal DA synthesis and metabolism were markedly increased by buspirone treatment; the maximum effective dose was 3.0 mg/kg, s.c., which caused a 400% increase. Extracellular single cell recordings showed that buspirone, administered intravenously, markedly increased substantia nigra DA neuronal impulse flow and potently reversed inhibition of DA cell impulse flow caused by systemic injection of apomorphine (5 to 10 μg/kg). Inhibition of DA cell impulse flow by iontophoresis of DA was reversed by iontophoretic administration of buspirone, but buspirone did not interfere with the ability of GABA to inhibit DA impulse flow. That buspirone interacts with receptor sites in addition to the DA autoreceptor was indicated by the finding that after DA receptor blockade with haloperidol, buspirone further enhanced DA neuronal impulse flow. Buspirone did not cause catalepsy and did not inhibit apomorphine-induced turning in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra, which indicated that the drug has minimal action at the classical postsynaptic DA receptor. These data suggest that (*a*) buspirone enhances DA neuronal activity, in part, by weakly inhibiting presynaptic DA receptors, and (*b*) buspirone has minimal effects on postsynaptic DA receptors.

Buspirone is a non-benzodiazepine drug which possesses potent anxiolytic activity (Goldberg and Finnerty, 1979). Despite exhibiting clinical potency equal to diazepam for reduction of anxiety, buspirone shows little affinity for or interaction with diazepam or γ-aminobutyric acid (GABA) binding in CNS tissue (Stanton et al., 1981). Stanton et al. (1981) also reported that buspirone lacks anticonvulsant and sedative activity. Thus, buspirone represents a novel class of anxiolytic drugs. The only site of pharmacological activity observed by Stanton and coworkers (1981) was in dopamine (DA) receptor binding assays. Buspirone was inactive in all other receptor binding assays (e.g., opiate, 5-hydroxytryptamine (5-HT)$_1$, 5-HT$_2$, α_1, α_2, β, H$_1$, H$_2$, etc.). Buspirone displaces a DA agonist (*N-n*-propyl-norapomorphine) and antagonist (spiperone) from striatal membranes with IC$_{50}$s of 20 and 290 nM, respectively. Because buspirone does not cause catalepsy, only weakly competes with spiperone binding, and is ineffective as an antipsychotic drug, Stanton et al. (1981) suggested that buspirone has minimal postsynaptic DA receptor blocking properties, but may act as a presynaptic DA autoreceptor agonist because of the higher affinity for the DA agonist binding site.

There are presynaptic autoreceptors on the DA cell bodies in the substantia nigra and on DA axon terminals

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(e.g., in the striatum). In the substantia nigra, microiontophoresis of DA and systemic administration of the DA agonist apomorphine inhibits DA neuronal impulse flow (Bunney et al., 1973; Aghajanian and Bunney, 1977; German et al., 1979). These effects are due to actions on the nigral DA neuronal autoreceptor (Skirboll et al., 1979). Cessation of DA impulse flow, which stops DA release, decreases DA availability at axon terminal autoreceptors and causes a marked activation of striatal tyrosine hydroxylase (Walters and Roth, 1976; Kehr et al., 1977). This *in vivo* activation, secondary to cessation of impulse flow, can be reversed by apomorphine. Furthermore, addition of apomorphine or DA to striatal synaptosomal preparations inhibits tyrosine hydroxylation (Iversen et al., 1976; Westfall et al., 1979). In all of these experiments, the inhibitory effect of apomorphine or DA can be blocked by antipsychotic drugs. If buspirone is an agonist at presynaptic DA autoreceptors, then it should mimic the effects of apomorphine in *in vivo* and *in vitro* autoreceptor test systems. The following series of experiments was designed to determine the agonist or antagonist activity of buspirone on the nigrostriatal dopaminergic neuronal system in the rat.

Materials and Methods

Biochemical experiments. Female Sprague-Dawley rats (Holtzman; 200 to 250 gm) were used. For biochemical assays the animals were killed by chloroform asphyxiation and the brains were rapidly removed and chilled in ice-cold saline. The brains were then cut according to the method of Glowinski and Iversen (1966) and the corpus striatum was removed. Synaptosomal tyrosine hydroxylase activity was determined using the method of Nagatsu et al. (1964). The 1,000 × *g* supernatant fluid from striatal homogenates (in 10 vol of 0.32 M sucrose) was used as the source of synaptosomes. Dowex 50 purified 3,5-[^{3}H]tyrosine (New England Nuclear) was used as substrate (200,000 cpm, 8×10^{-5} M) and the [^{3}H]H_2O formed in 30 min at 37°C was used as product. The [^{3}H]H_2O was separated from tyrosine, 3,4-dihydroxyphenylalanine (L-DOPA), and amines by passing the acidified incubation medium through Dowex 50 columns. The eluant was mixed with 13 ml of Beckman Readysolv HP scintillation fluid and counted in a Beckman LS 200 scintillation counter with external standardization.

Striatal concentrations of L-DOPA were determined by a modification of the method of Kehr et al. (1972), using batch alumina extraction and fluorophor development (McMillen and Shore, 1980). Striata from two animals were pooled for the L-DOPA assay. Tyrosine hydroxylase activity was estimated, *in vivo*, by the 30-min accumulation of L-DOPA following inhibition of L-aromatic amino acid decarboxylase with 100 mg/kg (i.p.) of NSD-1015 (3-hydroxybenzylhydrazine dihydrochloride). Concentrations of the dopamine metabolite, dihydroxyphenylacetic acid (DOPAC), were determined in striatum by organic solvent extraction and fluorophor development (Murphy et al., 1969).

Behavioral experiments. Rats were anesthetized with 400 mg/kg (i.p.) of chloral hydrate and placed in a stereotaxic instrument. The animals were pretreated with 5.0 mg/kg (i.p.) of desipramine to block the toxic effects of 6-hydroxydopamine (6-OHDA) on noradrenergic neurons. The substantia nigra was lesioned by infusing 4 μg of 6-OHDA in 2 μl into the nigra (2.2 mm anterior to ear bars, 2.0 mm lateral, and 7.2 mm below the dura according to the method of König and Klippel, 1963). After allowing 3 weeks for degeneration of the neurons, the rats were tested with apomorphine. Those rats exhibiting contralateral turning were used for subsequent experiments for effects of buspirone or turning. Turning rats had greater than 85% depletion of striatal dopamine ipsilateral to the lesion.

Electrophysiological experiments. For the electrophysiological experiments, male and female rats were anesthetized with chloral hydrate (400 mg/kg, i.p.) and the femoral or tail vein was catheterized. The animal was placed in a stereotaxic apparatus, and wound margins and pressure points were infiltrated with a long lasting local anesthetic (mepivacaine hydrochloride, 2%). Tungsten microelectrodes (2 to 4 megohms impedance) were used to record the extracellular action potentials of single DA cells in the intravenous drug experiments. For the microiontophoretic studies five-barrel micropipettes were used. The center barrel was filled with 2 M NaCl, saturated with fast green dye, and was used for recording. The tip of the electrode was broken back to a 4- to 5-μm diameter and then directly filled by injection of solutions into the various barrels. The presence of several fiberglass filaments (placed in each barrel prior to pulling) allowed the tips to become filled rapidly by capillary action (Tasaki et al., 1968). One side barrel was filled with 4 M NaCl, and this channel was used for automatic balancing (neutralizing) of tip current. The remaining side barrels were filled with (*1*) dopamine hydrochloride (0.2 M, pH 4.0), (*2*) buspirone (0.1 M, pH 4.0), and (*3*) GABA (0.05 M in 0.1 M NaCl, pH 4.0). During periods of base line unit recording, a negative retaining current of 10 nA was applied to each drug barrel. Drugs were ejected by passing a positive current of 5 to 40 nA through the appropriate barrel or barrels (Medical Systems BH-2 iontophoresis apparatus).

For substantia nigra zona compacta DA cell recording, a burr hole was drilled with its center 2.8 to 3.2 mm anterior to lambda and 1.8 to 2.2 mm lateral to the midline. The electrode was hydraulically lowered into the DA cell region. Extracellular action potentials were passed through a high impedance amplifier (Grass model P511, 0.3 to 3.0 kHz bandpass) and monitored on an oscilloscope and audio amplifier. Each action potential activated a Schmitt trigger, the output of which was counted, displayed, and stored in histogram form (MINC 11 computer, bin width 10 sec).

The anatomical location of the units tested was determined by passing a 20 μA negative current through the glass recording micropipette for 30 min. This resulted in the deposition of fast green dye in a discrete spot (Thomas and Wilson, 1965). When tungsten microelectrodes were used, a microlesion was made at this unit recording locus by passing 20 μA of positive current for 15 sec. Animals were then overdosed with Nembutal and perfused transcardially with neutral buffered formalin. The brain was sectioned on a freezing microtome at 50 μm and the sections were stained with cresyl violet.

Although the identity of a cell was determined retrospectively by histological examination, there were useful guidelines which aided in nigral DA unit identification. The cells exhibited long duration action potentials (> 2 msec) and fired between 1 and 8 Hz. These cells often fired in bursts with successive spikes within the burst exhibiting decreased spike amplitudes. These are the typical characteristics of DA-containing neurons (cf. Bunney et al., 1973; Grace and Bunney, 1980).

Drugs. The drugs used and their sources were: apomorphine hydrochloride, GABA, γ-butyrolactone (GBL), glutamate, NSD-1015, dopamine hydrochloride, and 6-hydroxydopamine hydrobromide (Sigma Chemical Co., St. Louis, MO); *d*-amphetamine and chlorpromazine hydrochloride (Smith, Kline & French Laboratories, Philadelphia, PA); haloperidol (McNeil Laboratories, Ft. Washington, PA); and buspirone hydrochloride (Mead Johnson Pharmaceutical Division, Evansville, IN). All doses refer to the free form of the drug except for NSD-1015.

Results

In vitro synaptosomal tyrosine hydroxylase activity. Buspirone was tested for its ability to inhibit synaptosomal tyrosine hydroxylase activity at concentrations from 10^{-8} to 10^{-4} M. A 25% inhibition of activity occurred at 10^{-4} M compared to IC_{50}s for apomorphine and DA of 5 × 10^{-7} and 2.5 × 10^{-6} M, respectively (McMillen, 1982). Since buspirone had very little agonist activity, the drug was tested as an antagonist of apomorphine inhibition. Figure 1 shows that a concentration of 2 × 10^{-6} M buspirone doubled the IC_{50} of apomorphine which indicated a K_B of 2.4 × 10^{-6} M. These data suggest that buspirone behaves as an antagonist of DA nerve ending autoreceptors.

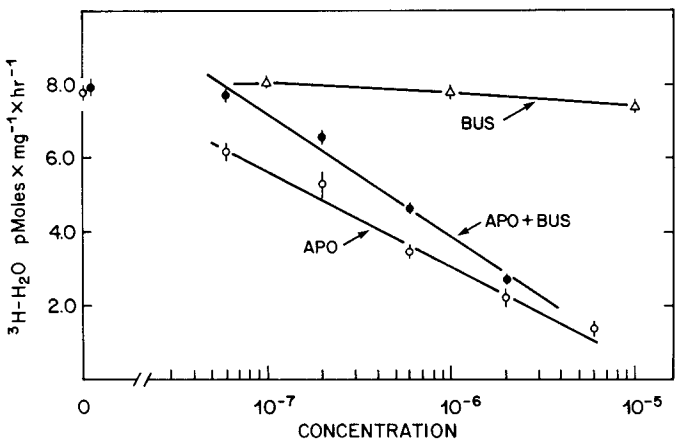

Figure 1. Effects of buspirone (*BUS*) or apomorphine (*APO*) on rat striatal synaptosomal tyrosine hydroxylase activity. The 1000 × *g* supernatant was incubated with 1.06 × 10^{-5} M [^{3}H] tyrosine and various concentrations of apomorphine (○), apomorphine plus 2 × 10^{-6} M buspirone (●), or buspirone alone (△). The [^{3}H]H_2O formed was used as an index of enzyme activity. Each *point* represents three to five duplicate determinations. Co-incubation of apomorphine with buspirone resulted in a significant reduction of the inhibition by apomorphine at each concentration ($p < 0.05$).

In vivo tyrosine hydroxylase activity. Buspirone was initially tested as an agonist in the presynaptic autoreceptor test of Walters and Roth (1976). However, buspirone (up to 10 mg/kg, i.p.) failed to inhibit the GBL-induced increase of L-DOPA accumulation which is normally found for DA autoreceptor agonists (data not shown). Table I compares buspirone with the DA antagonists, haloperidol and chlorpromazine, for blockade of the apomorphine actions on the DA autoreceptor. Buspirone significantly elevated L-DOPA accumulation above the level observed after apomorphine and GBL. The dose response curve for buspirone indicated that this drug was less potent than haloperidol but similar in potency to chlorpromazine.

Effects of buspirone on postsynaptic dopamine receptors. Buspirone in doses up to 10 mg/kg did not cause catalepsy. Catalepsy was assessed by the method of Shore and Dorris (1975), which allows for a graded response from no catalepsy to akinesia (rats' forepaws stay on a 3.0-cm peg) to marked rigidity (rats' forepaws stay on a 9.0-cm peg). All animals gave scores of 0, i.e., no catalepsy, regardless of buspirone dose. At 3 or 10 mg/kg, however, buspirone decreased locomotor activity.

Buspirone, at 3.0 mg/kg, s.c., caused a slight amount of hypomotility in both normal rats and rats with unilateral 6-OHDA lesions of the substantia nigra. Buspirone alone did not cause turning. Apomorphine (0.5 mg/kg, s.c.) was administered 30 min after buspirone. Despite the slight hypomotility caused by buspirone, these animals turned toward the contralateral side at a rate only slightly less than that produced by apomorphine alone (Table II). Thus, buspirone did not exhibit a marked antagonism of the classical postsynaptic dopamine receptor.

Effects of buspirone on dopamine synthesis and metabolism. Buspirone caused a dose-related increase of dopamine metabolism and *in vivo* tyrosine hydroxylase activity in the corpus striatum (Fig. 2). The elevation of

TABLE I

Comparison of buspirone with neuroleptic drugs in the in vivo presynaptic receptor test

The number of determinations for each group is shown in parentheses. The sequence of drug injection was: 0 min, test drug, s.c.; 5 min, 1.0 mg/kg, s.c., of apomorphine (APO); 10 min, 750 mg/kg, i.p., of γ-butyrolactone (GBL); 25 min, 100 mg/kg, i.p., of NSD-1015 (NSD); 55 min, kill. A plus sign after the test drug indicates that the drug injection sequence was continued.

		L-DOPA
		μg/gm ± sem
NSD		1.21 ± 0.07 (19)
GBL + NSD		3.54 ± 0.22[a] (8)
APO + GBL + NSD		1.02 ± 0.11 (6)
1.0 Haloperidol	+	2.42 ± 0.30[a] (6)
10.0 Chlorpromazine	+	1.87 ± 0.34[a] (7)
0.3 Buspirone	+	1.37 ± 0.10[b] (5)
1.0 Buspirone	+	1.54 ± 0.11[a] (6)
3.0 Buspirone	+	1.83 ± 0.24[a] (6)
10.0 Buspirone	+	2.05 ± 0.22[a] (7)

[a] $p < 0.01$; significantly different from APO + GBL + NSD (Dunnett's *t* test).

[b] $p < 0.05$; significantly different from APO + GBL + NSD (Dunnett's *t* test).

TABLE II

Effects of buspirone on apomorphine-induced turning in rats with unilateral 6-OHDA lesions of the substantia nigra

Rats were tested for apomorphine-induced turning 4 weeks after lesioning. Each rat was tested once with 0.5 mg/kg (s.c.) of apomorphine alone and once with 30 min pretreatment of 3.0 mg/kg (s.c.) of buspirone. One week separated treatments and order was randomized. The number of turns was counted between 15 and 20 min after injection. There was no statistical significance between treatments (paired t test, $p > 0.1$). The number of rats in each group is shown in parentheses.

	Turns/Minute ± SEM
Apomorphine	12.8 ± 2.3 (5)
Apomorphine + Buspirone	8.8 ± 3.8 (5)

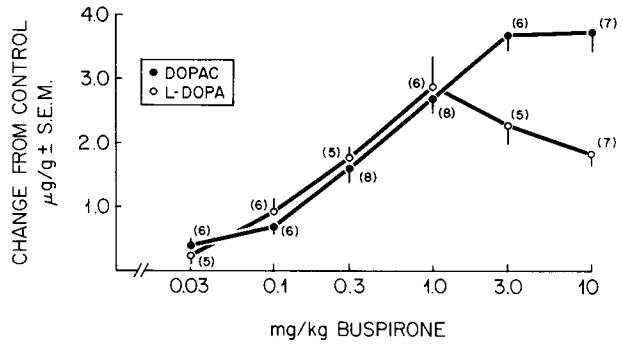

Figure 2. Effects of buspirone on striatal DA synthesis and metabolism. Striatal DOPAC (●) concentrations were determined 90 min after subcutaneous injection of buspirone and expressed as change from control (1.32 μg/gm). Striatal L-DOPA (○) accumulation was determined 30 min after decarboxylase inhibition with 100 mg/kg of NSD-1015, i.p. Buspirone was injected 30 min before NSD-1015 and concentrations were expressed as change from control (1.21 μg/gm/30 min). The number of determinations is shown in *parentheses*.

DOPAC concentrations reached maximum at a dose of 3.0 mg/kg, (s.c.) of buspirone. Enhanced L-DOPA accumulation closely followed enhanced DOPAC concentrations but fell off at 3.0 and 10 mg/kg. The maximum increase caused by buspirone (about 4-fold) was similar to that observed with haloperidol which required only 0.3 mg/kg, s.c., to produce the same effect (McMillen, 1980). Thus, buspirone was able to increase DOPAC concentrations to the same extent as a classical neuroleptic drug.

Effects of buspirone on dopamine cell impulse flow. Forty rats were used (36 male, 4 female), and in the intravenous drug experiments, one DA cell was tested in each rat. Buspirone alone (0.1 to 2.0 mg/kg) increased DA cell firing rates above base line in 9 cells (4 of the 9 animals were female; see Fig. 3*A*), had no effect on 3 cells, and decreased the firing rate of 1 cell. Often the increase in firing showed a transient (2- to 3-min) dramatic increase followed by a lower sustained tonic increase (15 to 20 min, after which the experiment was terminated), which probably represents redistribution of the drug. Buspirone (0.01 to 1.0 mg/kg) also reversed apomorphine (10 μg/kg, 6 of 6 cells; see Fig. 3*B*) and *d*-amphetamine (0.5 to 1.0 mg/kg, 5 of 5 cells) inhibitions of DA cell firing and increased cell firing to or above base line. Furthermore, buspirone increased DA cell firing

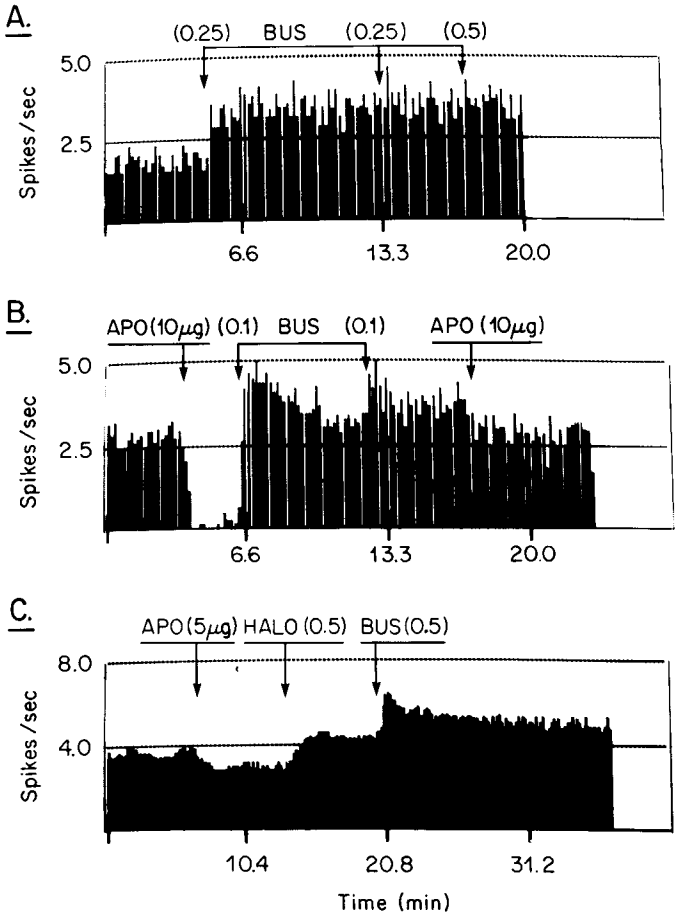

Figure 3. Effects of buspirone on the firing rate (spikes/second) of substantia nigra DA-containing neurons. *A*, Buspirone (*BUS*; 0.25, 0.25, and 0.5 mg/kg, i.v.) increased the firing rate of this neuron above base line. *B*, Apomorphine (*APO*: 10 μg/kg, i.v.) decreased the firing rate of this neuron, and this effect was reversed by BUS (0.1 mg/kg, i.v.). A subsequent injection of APO was much less effective in decreasing DA impulse flow after BUS. *C*, The firing rate of this DA neuron was decreased by APO (5 μg/kg, i.v.), and this effect was reversed by the DA receptor blocker haloperidol (*HALO*; 0.5 mg/kg, i.v.). A subsequent injection of BUS (0.5 mg/kg, i.v.) markedly increased DA neuronal impulse flow above the level produced by HALO.

rates above the level produced by a prior injection of haloperidol (0.5 to 1.0 mg/kg) in 8 of 10 cells tested (see Fig. 3*C*),[3] whereas after buspirone (0.5 to 2.0 mg/kg) haloperidol (0.5 mg/kg) had little effect on DA cell firing (10 of 10 cells).

Iontophoresis of DA (10 to 30 nA) onto DA neurons consistently reduced cell firing rate in a dose-dependent manner (9 of 9 cells). Iontophoresis of buspirone alone (8 to 25 nA) had little effect on DA cell firing rate (in 8 of 9 cells; 1 cell increased 21%) but always blocked or attenuated the effects of DA (8 of 8 cells; Fig. 4*A*). These effects of buspirone are similar to those of the DA recep-

[3] Apomorphine produced a relatively small decrease in impulse flow in this cell (i.e., 17% decrease), as is typical of caudal nigral neurons. More rostral nigral neurons decrease their firing rates dramatically after apomorphine (Shepard and German, 1982).

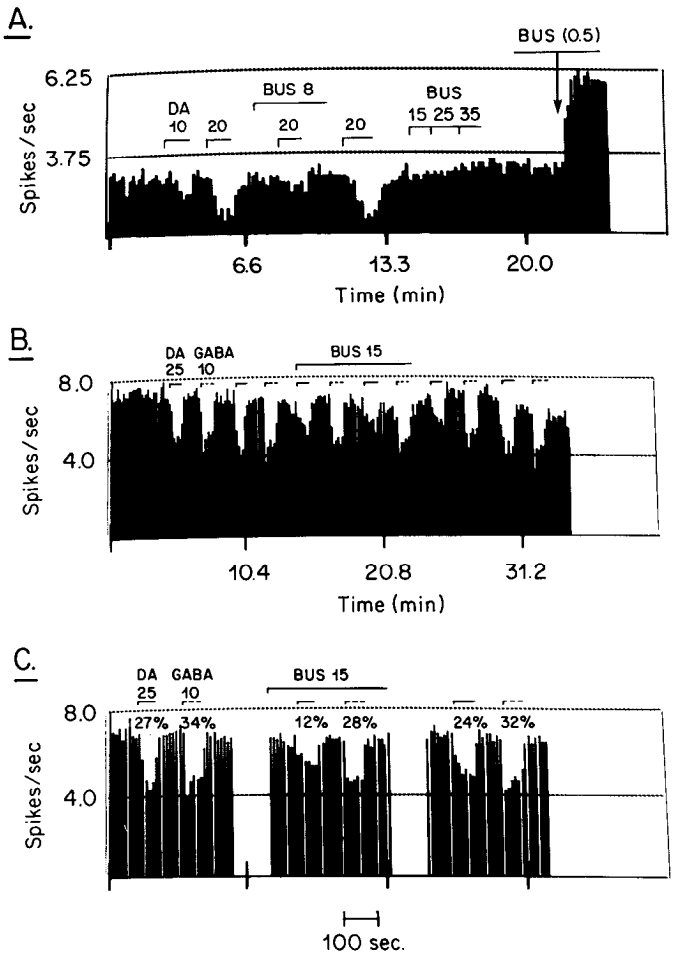

Figure 4. Effects of microiontophoresed buspirone (*BUS*) on the firing rate (spikes/second) of substantia nigra DA-containing neurons. *A*, BUS (8 nA) blocked the inhibitory effects of microiontophoresed DA on nigral cell firing rate. BUS alone at high current slightly increased DA cell firing. The firing rate of this cell was markedly increased by intravenous BUS (0.5 mg/kg). *B*, BUS (15 nA) substantially attenuated the inhibitory effects of DA (25 nA) with little effect on GABA (10 nA). Both DA- and GABA-induced inhibitions were submaximal. *C*, Summary histogram illustrating the effects of BUS on DA and GABA inhibition from *B*. The summary histogram represents the average firing rate/10 sec before, during, and after the two drug applications of DA or GABA. DA produced a 27% inhibition and GABA produced a 34% inhibition of cell firing. During the simultaneous application of BUS, DA only produced 12% inhibition (a significant reduction in the inhibitory effect produced by DA, $p < 0.001$), while GABA still produced 28% inhibition. After BUS was turned off, DA and GABA produced inhibitions comparable to pre-BUS levels.

tor blocker, trifluoperazine (Aghajanian and Bunney, 1977). Iontophoresis of buspirone at currents that reduced the DA response by at least 50% did not markedly alter the inhibitory effects of GABA (6 of 6 cells; Fig. 4, *B* and *C*).

Discussion

Buspirone had marked effects on dopaminergic neurotransmission. Stanton et al. (1981) reported that buspirone had high affinity for the DA agonist (*N*-*n*-norpropylapomorphine) and a lower affinity for antagonist (spiperone) binding sites. Because buspirone's IC_{50} for the agonist site was 15-fold less than that of the antagonist site, they suggested that buspirone may be a presynaptic DA agonist. The suggestion was derived from the hypothesis of Seeman and co-workers (Nagy et al., 1978; Titeler et al., 1979) that DA agonist binding occurs at DA nerve ending autoreceptors. Our experiments with buspirone, in both *in vivo* and *in vitro* test systems for DA autoreceptor activity, clearly demonstrated that buspirone is without presynaptic agonist activity.

Buspirone does have antagonist activity at DA autoreceptors. Buspirone shifted to the right the apomorphine inhibition curve in the synaptosomal tyrosine hydroxylase test with a calculated affinity K_B of 2.4 μM. The affinity of buspirone is similar to that of the relatively weak DA antagonist, chlorpromazine (1.2 μM; McMillen, 1982). The data in Table I show that buspirone behaves as an antagonist in the Walters and Roth (1976) *in vivo* presynaptic receptor test with a potency slightly greater than that of chlorpromazine. As expected from a drug with such activity, buspirone reverses the inhibition of DA impulse flow caused by apomorphine or microiontophoresed DA. Thus, buspirone appears to have presynaptic autoreceptor antagonist activity similar to that of other weak autoreceptor antagonists.

Buspirone increased DA cell impulse flow to a greater extent than did haloperidol. Buspirone blocked the DA autoreceptor to the DA cell body, as evidenced by the fact that it selectively blocked the inhibitory effects of microiontophoresed DA, as does the potent pre- and postsynaptic DA receptor blocker, haloperidol (see Aghajanian and Bunney, 1974). That buspirone is influencing more than just DA presynaptic receptor sites was indicated when buspirone further enhanced DA impulse flow after DA receptor blockade with a large dose of haloperidol (Fig. 3*C*). Thus, buspirone may have a site of action, in addition to the DA autoreceptor, which produces an increase in nigrostriatal DA impulse flow. Such enhancement of DA cell impulse flow is a contributing factor to the ability of buspirone to increase striatal DA synthesis and metabolism.

Buspirone appears to weakly block striatal postsynaptic DA receptors. Buspirone did not markedly inhibit apomorphine-induced turning in rats with unilateral lesions of the substantia nigra. However, large doses of buspirone did cause hypoactivity. But catalepsy, a typical response to large doses of DA postsynaptic receptor blockers, was never observed. Furthermore, buspirone is ineffective as an antipsychotic drug in doses up to 2.0 gm/day, but it is a weak inhibitor of stimulant-induced stereotypies (Stanton et al., 1981). Buspirone must have some postsynaptic DA receptor-blocking properties since it markedly increases DA cell impulse flow, yet it does not produce stimulant-like behavior (i.e., locomotion or stereotypies). These observations indicate that buspirone has weak effects at the classical postsynaptic DA receptor associated with the behavioral and clinical effects that are observed with classical antipsychotic drugs (cf. Seeman, 1980). The antipsychotic drug, molindone, is the only other drug known to be a dose-preferential antagonist for the DA autoreceptor (Alander et al., 1980).

What is the anti-anxiety mechanism of buspirone? There are at least two mechanisms which could explain the therapeutic actions of anxiolytic drugs. Benzodiazepine anxiolytics are thought to produce their therapeutic effects by potentiating GABA inhibition at specific benzodiazepine-related GABA receptor sites (see Costa and Guidotti, 1979). However, buspirone does not interact with benzodiazepine or GABA binding (Stanton et al., 1981). Some maintain that anxiolytics, including benzodiazepines, produce their effects by decreasing locus ceruleus impulse flow or blocking norepinephrine output (Redmond, 1977). However, we find that buspirone neither decreases locus ceruleus impulse flow nor decreases cortical norepinephrine metabolism, as does diazepam (Sanghera et al., 1982). Clearly, buspirone represents a novel anxiolytic whose mechanism of action is presently unknown.

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