

# Preclinical Neurochemical and Electrophysiological Profile of 1192U90, A Potential Antipsychotic

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1192U90 was submitted to receptor binding and monoamine uptake assays. It bound potently at serotonin 5-HT<sub>2</sub>, dopaminergic D<sub>2</sub>, serotonin 5-HT<sub>1A</sub>, and adrenergic  $\alpha_1$  and  $\alpha_2$  receptors. It also bound to dopaminergic D<sub>1</sub>, serotonin 5-HT<sub>3</sub>, serotonin 5-HT<sub>4</sub>, and sigma sites, albeit with lower affinity. It was essentially inactive at 22 other sites, including those for cholinergic M<sub>1</sub> and M<sub>2</sub>. It weakly inhibited uptake of <sup>3</sup>H-norepinephrine, <sup>3</sup>H-serotonin and <sup>3</sup>H-dopamine. Acute doses of 1192U90 (5 and 20 mg/kg P.O.) increased whole-brain levels of dopamine metabolites but did not affect levels of norepinephrine, dopamine, and serotonin.

Subcutaneous injection of 1192U90 (0.8 mg/kg/day) and clozapine (20 mg/kg/day) for 28 days preferentially decreased the number of spontaneously active dopamine cells in the ventral tegmental area (VTA) but not the

substantia nigra (SN) of rats, as measured by population sampling. This outcome is characteristic of atypical antipsychotics like clozapine. Acute injections of 1192U90 reversed the rate-inhibiting effects of microiontophoretically applied dopamine and intravenously injected apomorphine and d-amphetamine on dopamine cell firing. Intravenous injection or iontophoretic application of 1192U90 or the 5-HT<sub>1A</sub> agonist ( $\pm$ )8-OH-DPAT inhibited the firing rates of dorsal raphe nucleus (DRN) neurons in rats, and the effects of both compounds were blocked by iontophoretically applied S(-) propranolol, a 5-HT<sub>1A</sub> antagonist. The results suggest that 1192U90 is a preferential dopamine D<sub>2</sub> antagonist as well as a 5-HT<sub>1A</sub> agonist that may prove to be an atypical antipsychotic. [*Neuropsychopharmacology* 15:217-230, 1996]

**KEY WORDS:** Neurotransmitter; Receptor; Uptake; HPLC; Dopamine turnover; Atypical antipsychotic; Single-unit recording; Dopamine; Serotonin; Substantia nigra; Ventral tegmental area; Dorsal raphe nucleus

There is substantial need for an agent that can manage the symptoms of schizophrenia. Although the typical antipsychotics such as chlorpromazine and haloperidol

were a major advance, they were effective in only a portion of the patient population and were ineffective for the negative symptoms of schizophrenia (Lieberman 1993). The side effect profile of these drugs was poor; severe extrapyramidal side effects, including dystonia, Parkinsonism, akathisia, and tardive dyskinesia were common (Tarsy 1983). In some instances, tardive dyskinesia remained even after discontinuation of drug therapy (Tarsy 1983).

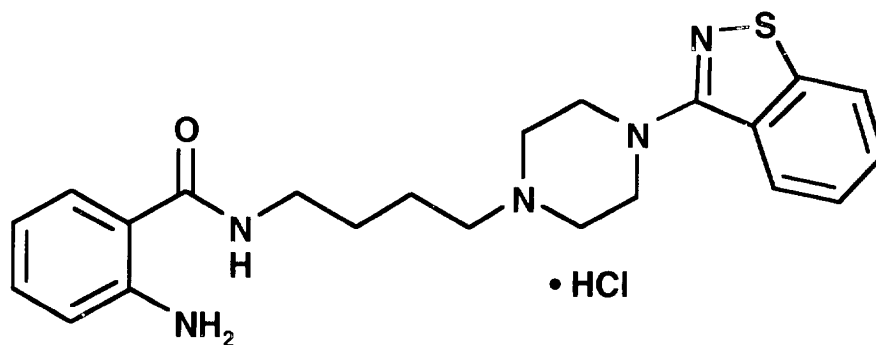
Clozapine is an atypical antipsychotic in that it is effective against both positive and negative symptoms (Kane et al. 1988; Meltzer et al. 1989; Lieberman 1993) and does not cause Parkinsonism, dystonia, or tardive dyskinesia (Gerlach et al., 1974; Shopsin et al. 1979;

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**Figure 1.** 1192U90, 2-amino-N-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide.



Claghorn et al. 1987; Casey 1989). However, it has other side effects, including seizures, hypotension, sedation, and sialorrhea (Shopsin et al., 1979; Meltzer 1992). These are likely to be due to the fact that clozapine has actions at a variety of neurotransmitter receptors in brain, including histamine<sub>1</sub> and muscarinic receptors (Coward 1992). The major limiting side effect of clozapine is its association with agranulocytosis (Idänpään-Heikkilä et al. 1975; Griffith and Saameli 1975; Lieberman et al. 1988). There are no drugs on the market that address both the positive and negative symptoms of schizophrenia without the risk of severe, debilitating side effects.

1192U90 is active in animal models that predict clinical antipsychotic efficacy (Figure 1). Differing from the typical antipsychotic medications, 1192U90 is similar to the atypical agent clozapine in that it does not block apomorphine-induced stereotypy in rats, nor does it cause catalepsy, which indicates that it may have a reduced side effect liability (Coward 1992; Rigdon et al. 1996). 1192U90 blocks conditioned avoidance responding in rats (Rigdon et al. 1996) and has dopamine antagonist effects on animal behavior. It blocks apomorphine-induced climbing in mice and apomorphine-induced rotation in rats with unilateral lesions of the nigrostriatal system (Rigdon et al. 1996). In other behavioral tests, 1192U90 acts like a 5-HT<sub>2</sub> antagonist in that it prevents 5-HTP-induced head shakes in rats (Rigdon et al. 1996). Like 5-HT<sub>1A</sub> agonists, it also increases punished responding in pigeons and cork gnawing in rats (Rigdon et al. 1996).

The purpose of this report is to characterize and describe the neurochemical and electrophysiological attributes of 1192U90.

## METHODS

### Neurochemistry

**Receptor Binding.** Radioligand receptor binding assays were adapted from previously published methods (Table 1). Radioligands were obtained from DuPont NEN (Boston, MA), Amersham (Arlington Heights, IL) or

Moravek Biochemicals (Brea, CA). Standards and ligands used to determine non-specific binding were obtained from Research Biochemicals International (Natick, MA) and Sigma Chemical Co. (St. Louis, MO). *K<sub>i</sub>* values were determined using the Cheng-Prusoff equation (Cheng and Prusoff 1973).

**Uptake.** The effect of 1192U90 on the net uptake of norepinephrine (NE), dopamine (DA); and serotonin (5-HT) was measured essentially as described previously (Ferris and Tang 1979; Slotkin et al. 1986). The hypothalamus (5-HT and NE uptake) or striatum (DA uptake) from rats were homogenized in 18 volumes of Sucrose-Tris buffer (0.3 M sucrose, 25 mM Tris, pH 7.4) by a Potter-Elvehjem homogenizer with a Teflon pestle. The homogenate was centrifuged at 1,000 × g for 10 minutes at 4°C. The supernatant was removed and used in the assay. 1192U90 was pre-incubated with the tissue in modified Krebs-Henseleit buffer (118 mM NaCl, 5 mM KCl, 25 mM NaHCO<sub>3</sub>, 1.2 mM NaH<sub>2</sub>PO<sub>4</sub>, 1.2 mM MgSO<sub>4</sub>, 11 mM glucose, 2.5 mM CaCl<sub>2</sub>, pH 7.4) at 37°C for 5 minutes. <sup>3</sup>H-Neurotransmitter was added and allowed to incubate for an additional 5 minutes. <sup>3</sup>H-Neurotransmitter that had been transported into the synaptosomes was separated from <sup>3</sup>H-neurotransmitter remaining outside by rapid filtration over GF/B filters followed by three rapid washes with ice-cold modified Krebs-Henseleit buffer. Filters were placed in Ready-Safe scintillation cocktail and counted on a Packard Tri-Carb Scintillation Counter. Nonspecific uptake was defined as uptake at 0°C.

**Biogenic Amine Levels.** Adult male Wistar rats (*n* = 7 per group) were orally dosed with haloperidol (1 mg/kg), 1192U90 (5 or 20 mg/kg, representing the ED<sub>50</sub> and four times the ED<sub>50</sub> for antipsychotic efficacy in behavioral tests, Rigdon et al. 1996), or 0.5% methylcellulose vehicle. One hour later they were sacrificed by decapitation, and whole brains were immediately removed to dry ice. The tissues were stored at -80°C until analysis (≤1 week).

Biogenic amines were extracted by homogenizing

**Table 1.** Receptor Binding Methods

Receptor	<sup>3</sup> H-Ligand (nM)	Species	Tissue	Ligand Used to Determine Non-specific Binding	Reference
Dopaminergic D <sub>1</sub>	SCH-23390 (0.2)	Rat	Striatum	SCH-23390	Billard et al., 1984
Dopaminergic D <sub>2</sub> /D <sub>3</sub>	raclopride (1)	Rat	Striatum	Sulpiride	Dewar et al., 1989
Serotonergic 5-HT <sub>1A</sub>	8-OH-DPAT (0.2)	Rat	Hippocampus	Serotonin	Peroutka, 1986
Serotonergic 5-HT <sub>2</sub>	Ketanserin (0.5)	Rat	Frontal cortex	Ketanserin	Leysen et al., 1982
Serotonergic 5-HT <sub>3</sub>	BRL 43694 (0.5)	Rat	Cerebral cortex	N-Methylquipazine	Nelson and Thomas, 1989
Serotonergic 5-HT <sub>4</sub>	GR 113808 (0.1)	Rat	Striatum	Serotonin	Grossman et al., 1993
Adrenergic alpha <sub>1</sub>	WB-4101 (0.2)	Rat	Whole brain	Norepinephrine	Greenberg et al., 1976
Adrenergic alpha <sub>2</sub>	Yohimbine (1)	Rat	Cerebral cortex	Norepinephrine	Rouot et al., 1982
Adrenergic beta <sub>1</sub>	[ <sup>125</sup> I]-Pindolol (0.2) with unlabeled ICI-118,551	Rat	Cerebral cortex	Isoproterenol	Kalaria et al., 1989; Minneman et al., 1979
Adrenergic beta <sub>2</sub>	[ <sup>125</sup> I]-Pindolol (0.2) with unlabeled ICI-89,406	Rat	Cerebral cortex	Isoproterenol	Kalaria et al., 1989; Minneman et al., 1979
Cholinergic M <sub>1</sub>	Pirenzepine (1)	Rat	Forebrain	Atropine	Watson et al., 1983
Cholinergic M <sub>2</sub>	QNB (0.05)	Rat	Heart	Atropine	Watson et al., 1983
Cannabinoid	WIN 55,212-2 (1)	Rat	Cerebellum	WIN 55,212-2	D'Ambra et al., 1992
Sigma	SKF 10047 (3)	Guinea pig	Whole brain	Ethylketo-cyclazocine	Tam, 1983
Neurotensin	Neurotensin (2)	Rat	Forebrain	Neurotensin	Goedert et al., 1984
Neurokinin <sub>1</sub> (Substance P)	Substance P (1.4)	Rat	Submaxillary glands	Substance P	Bahouth and Musacchio, 1985
Neurokinin <sub>2</sub> (NK <sub>A</sub> )	[ <sup>125</sup> I]-Neurokinin A (0.1)	Bovine	Duodenum	Neurokinin A	Burcher et al., 1986
Neurokinin <sub>3</sub> (NK <sub>B</sub> )	Eledoisin	Rat	Cerebral cortex	Eledoisin	Mussap and Burcher, 1990
Benzodiazepine	diazepam (1.5)	Rat	Forebrain	Diazepam	Marangos and Martino, 1981
Leukotriene D <sub>4</sub>	Leukotriene D <sub>4</sub> (0.4)	Guinea pig	Lung	Leukotriene D <sub>4</sub>	Cheng and Townley, 1984
Cholecystokinin <sub>8</sub>	CCK <sub>8</sub> (0.2)	Mouse	Cerebral cortex	CCK4	Saito et al., 1981
Platelet activating factor	PAF (0.2)	Rabbit	Platelet	PAF	Hwang et al., 1986
Angiotensin II	Angiotensin II (1)	Rat	Liver	Angiotensin II	Lynch et al., 1985
Ca <sup>++</sup> channel (dihydropyridine)	Nitrendipine (0.2)	Rat	Cerebral cortex	Nifedipine	Gould et al., 1982
Ca <sup>++</sup> channel (phenylalkylamine)	Verapamil (1)	Rat	Heart	Verapamil	Reynolds et al., 1986
Ca <sup>++</sup> channel (Ryanodine)	Ryanodine (3.3)	Dog	Heart	Ryanodine	Rardon et al., 1990
ATP-dependent K <sup>+</sup> channel	Glibenclamide (0.1)	Rat	Whole brain	Glibenclamide	Gopalakrishnan et al., 1991
ATP-dependent K <sup>+</sup> channel	Glibenclamide (0.06)	Rat	Heart	Glibenclamide	Gopalakrishnan et al., 1991
GABA Cl <sup>-</sup> channel	[ <sup>35</sup> S]-TBPS (1)	Rat	Cerebral cortex	Picrotoxinin	Eshleman and Murray, 1990
Endothelin A	125I-ET-1 (0.03)	Rat	Cerebellum	ET-1	Waggoner et al., 1992
Endothelin B	125I-ET-1 (0.03)	Rat	Cerebral cortex	ET-1	Waggoner et al., 1992
Adenosine transporter	Dipyridamole (4)	Guinea pig	Whole brain	Dipyridamole	Marangos and Deckert, 1987

each tissue sample of a known weight in 0.1 M cysteine in 5% trichloroacetic acid along with a known amount of 3,4-dihydroxybenzylamine (DHBA) as an internal standard. The homogenate was centrifuged at 48,000 × g for 20 minutes at 5°C. The supernatant was removed

and centrifuged again to ensure removal of all particulates. A 10-μl aliquot of the resulting supernatant was analyzed by HPLC coupled to an electrochemical detector. Samples were kept at 0 to 5°C throughout preparation.

Neurotransmitters and their metabolites were separated on a Chromanetics Spherisorb ODS 2 stationary phase (4.5 × 150 mm, 5- $\mu$ m particles) at 35°C. Analytes were eluted at 1.0 ml/minute with a mobile phase consisting of 60 mM NaH<sub>2</sub>PO<sub>4</sub>, 31 mM citric acid, 0.27 mM EDTA, 1.0 mM 1-octane sulfonic acid (sodium salt), and 16% methanol in HPLC grade water. The methanol was added after the pH of the aqueous component was adjusted to 3.0. Each sample was introduced to the system via a refrigerated autoinjector kept at 5°C. The analytes were monitored by amperometric electrochemical detection at a potential of 800 mV. The resulting data were collected on a Perkin Elmer Model 1020 Electronic Integrator. Brain amine levels were calculated based on the recovery of the internal standard. The entire system was recalibrated after every five samples.

## Electrophysiology

**General Methods.** 1192U90 was synthesized by Dr. Mark Norman at Burroughs Wellcome Co. ( $\pm$ )-8-hydroxydipropylaminotertralin (8-OH-DPAT), *S*(-)-propranolol hydrochloride, and 3-hydroxytyramine (dopamine) were obtained from Research Biochemicals International (Natick, MA). Chloral hydrate and apomorphine were obtained from Sigma Chemical Co. (St. Louis, MO). *d*-Amphetamine was a gift from Smith Kline & French (Philadelphia, PA). Haloperidol was a gift from McNeil Pharmaceutical (Raritan, NJ). Clozapine was gift from Sandoz Pharmaceuticals (East Hanover, NJ).

Male CD rats weighing 200 to 300 g (Charles River Laboratories, Raleigh, NC) served as subjects. For single-unit and microiontophoresis experiments, they were anesthetized with chloral hydrate 400 mg/kg IP and secured in a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA). A lateral tail vein was cannulated for drug injections. Additional chloral hydrate was given IV as needed to maintain anesthesia. Body temperature was maintained at 36 to 38°C with a heating pad. The skull was exposed and a small hole was drilled overlying the area of the substantia nigra (SN), ventral tegmental area (VTA), or dorsal raphe nucleus (DRN). Single- or multi-barrel electrodes were prepared and were lowered through the hole in the skull to the appropriate brain region by an electric microdrive (Burleigh Instruments, Fishers, NY).

Electrical signals of single-unit discharges were passed through a high-input impedance amplifier and filtered through a window discriminator with bandpass settings at 400 Hz and 2 kHz (Fintronic WDR-420, Fintronic Inc., Orange, CT). Discriminator output was displayed on an oscilloscope and amplified through an audio monitor. Neuronal activity was counted, summed over 10-sec bins, plotted by a Gould recorder, and printed by a Datel printer. During microiontophoresis experiments, current balancing, holding currents, and ejection

currents were controlled by a Fintronics E-104 microiontophoresis unit.

After the last electrode penetration in any experiment, 25 mA of negative current was delivered through the electrode tip to deposit dye at the site of recording. Rats were euthanized under chloral hydrate anesthesia by injection of an air embolus. Brains were removed and fixed in 10% phosphate buffered formalin. Visualization of dye spots and electrode tracks on brain slices confirmed proper electrode placement.

### *Dopamine Neurons: Antagonism of the Inhibitory Effects of Apomorphine and d-Amphetamine.*

Dopamine neurons were located within the stereotaxic coordinates 2 to 2.4 mm lateral (L) from the midline suture, 2.8 to 3.4 mm anterior (A) from lambda, and 6.0–8.5 mm ventral (V) from the surface of the brain for SN, or 0.4 to 1.0 mm L, 3.0 to 3.4 mm A, and 6.0 to 8.5 mm V for VTA. Dopamine neurons in each brain region were identified by standard electrophysiological criteria: slow firing rate (1–10 spikes/sec) with regular or bursting firing patterns, of over 2-sec duration with notched bi- or triphasic wave form (Aghajanian and Bunney 1977; White and Wang 1984; Cox et al. 1988).

In experiments with IV drug injection, single-barrel glass electrodes were used to record neuronal activity. After a neuron identified as a dopamine cell was encountered, stable baseline firing was recorded for 3 to 5 minutes. Doses of apomorphine (20–50  $\mu$ g/kg cumulative) or *d*-amphetamine (0.5–1.5 mg/kg cumulative) were injected every 1 or 2 minutes to produce partial but nearly complete inhibition of firing rate. Doses of 1192U90 (6.25–200  $\mu$ g/kg cumulative) or haloperidol (5–100  $\mu$ g/kg cumulative) were subsequently injected. Responses to the agonists and 1192U90 or haloperidol on firing rates were determined by averaging the final 60 seconds of each dose interval and expressing it as a percentage of the baseline. Responses were then averaged across doses and expressed as a mean  $\pm$  standard error of the mean (SEM) for each group of rats.

In iontophoresis experiments, the central barrel of a five-barrel glass microelectrode (Activational Systems, Inc., Warren, MI) was filled with 2M NaCl containing 1% Pontamine sky blue dye (impedance 3–12 M $\Omega$ ) and was used for recording neuronal firing. One side barrel was filled with 0.2 M NaCl and used for current balancing (in vitro impedance  $\sim$ 20 M $\Omega$ ). One side barrel contained dopamine (0.1 M, pH 4) that was applied to inhibit dopamine cell firing. Another barrel contained 1192U90 (1 mM, pH 3). The in vitro impedance of the drug-containing side barrels was between 60 and 110 M $\Omega$ . After the baseline firing rate of a cell was recorded, dopamine was first applied alone (10–40 nA) for 60 seconds and the response was recorded. After the firing rate had returned to baseline values, 1192U90 (10–20

**Table 2.** Receptor Binding Results:  $K_i$  in nM (or % inhibition at 10  $\mu$ M)

Receptor	1192U90	Risperidone	Clozapine
Dopaminergic D <sub>1</sub>	140	320	84
Dopaminergic D <sub>2</sub> /D <sub>3</sub>	22	16	200
Serotonergic 5-HT <sub>1A</sub>	2.5 <sup>d</sup>	290 <sup>a</sup>	1300 <sup>a</sup>
Serotonergic 5-HT <sub>2</sub>	1.5 <sup>b</sup>	0.7 <sup>b</sup>	13 <sup>b</sup>
Serotonergic 5-HT <sub>3</sub>	1300		
Serotonergic 5-HT <sub>4</sub>	2400	480	>10000
Adrenergic alpha <sub>1</sub>	0.26	3.3	41
Adrenergic alpha <sub>2</sub>	11 <sup>c</sup>	11 <sup>c</sup>	82 <sup>c</sup>
Adrenergic beta <sub>1</sub>	[12]		
Adrenergic beta <sub>2</sub>	[25]		
Sigma	470		
Cholinergic M <sub>1</sub>	[51]		40 <sup>d</sup>
Cholinergic M <sub>2</sub>	[51]		4 <sup>d</sup>

<sup>a</sup>  $K_i$  calculated by using  $K_j$  from Gozlan et al. 1983.

<sup>b</sup>  $K_i$  calculated by using  $K_j$  from Leysen et al. 1982.

<sup>c</sup>  $K_i$  calculated by using  $K_j$  from Rouot et al. 1982.

<sup>d</sup> IC<sub>50</sub>.

nA) was applied for 180 seconds and a pulse of dopamine was applied during seconds 60 to 120 (i.e., during the second minute) of the application. The effects of dopamine alone and with 1192U90 were determined by expressing the mean firing rate during iontophoretic ejection as a percentage of the baseline rate. Responses were averaged across ejection currents and expressed as a mean  $\pm$  SEM.

**Dopamine Neurons: Population Sampling after Acute and Chronic Administration of 1192U90 and Clozapine.** 1192U90 (0.8 mg/kg/day) or clozapine (20 mg/kg/day) was injected SC either acutely (2 hours before the first electrode penetration) or chronically for 28 days with the last dose given 2 hours before the first electrode penetration. The dose of 1192U90 was chosen because it is the ED<sub>84</sub> by the subcutaneous route in the rat conditioned avoidance test (Rigdon et al. 1996). The dose of clozapine was chosen from the literature to allow comparison with published values (White and Wang 1983b). The experimenter conducting population sampling studies was not blind to treatment conditions.

A single-barrel glass electrode was slowly advanced

**Table 3.** Receptor Binding Results: IC<sub>50</sub> (or % inhibition at 10  $\mu$ M)

Receptor	1192U90
Adenosine transporter	[14]
Angiotensin II	[3]
ATP dependent	[0]
K <sup>+</sup> channel (brain)	
ATP dependent	[0]
K <sup>+</sup> channel (heart)	
Benzodiazepine	[2]
Ca <sup>++</sup> channel (phenylalkylamine)	6800
Ca <sup>++</sup> channel (dihydropyridine)	[18]
Ca <sup>++</sup> release channel (Ryanodine)	[7]
Cannabinoid	[10]
Cholecystokinin <sub>8</sub>	[3]
Endothelin A	[3]
Endothelin B	[6]
GABA Cl <sup>-</sup> channel	[4]
Leukotriene D <sub>4</sub>	[2]
Neurotensin	[0]
Neurokinin <sub>1</sub>	[2]
Neurokinin <sub>2</sub>	[36]
Neurokinin <sub>3</sub>	[8]
Platelet activating factor	[29]

(5–10 microns/sec) into a predetermined stereotaxic array over the SN or VTA. Penetrations were repeated for 12 tracks at identical stereotaxic coordinates in each rat. Each penetration was separated by 0.2 mm, and the order of first penetration (SN or VTA) was reversed for each successive rat.

Spontaneously active dopamine neurons were counted, and the firing of each neuron was recorded for several minutes. Results are reported as the number of spontaneously active cells/track/rat and the mean spontaneous firing rate (each expressed as a percentage of the corresponding value from a vehicle control group).

**Serotonin Neurons: Effects of Acute 1192U90 on Dorsal Raphe Unit Activity.** Neurons of the DRN were located within the stereotaxic boundaries 0.0–0.2 mm (L), 0.3–0.7 mm (A), and 5.5–6.5 mm (V). Serotonin neurons were identified by electrophysiological characteristics: slow firing rates (0.2–3 spikes/sec) and wide positive-

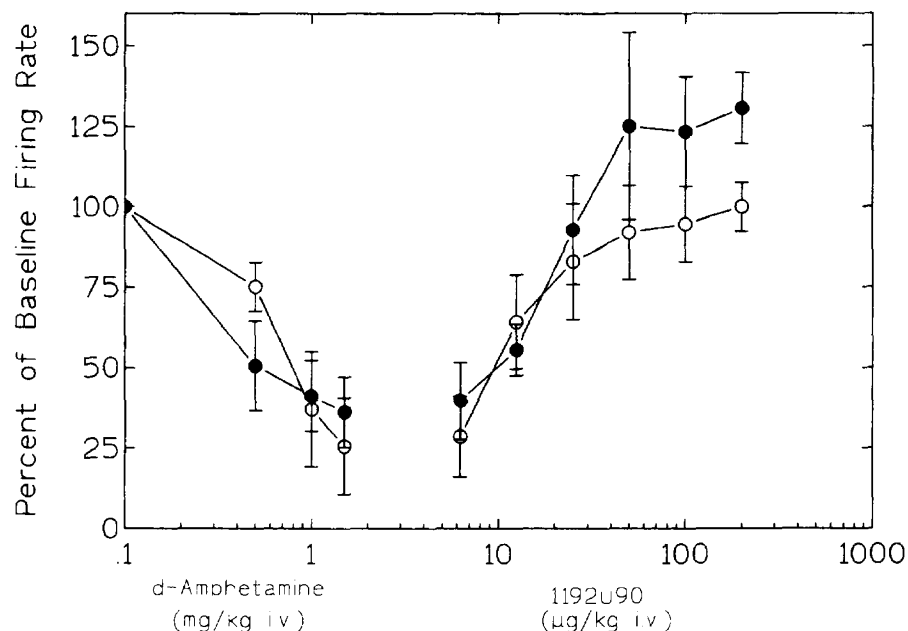
**Table 4.** Effects of Haloperidol or 1192U90 on the Concentration of Rat Brain Biogenic Amines Biogenic Amine Levels (pmol/mg of wet weight)

Treatment Group	NE	DA	DOPAC	HVA	5-H <sub>1AA</sub>	5-HT
Control	6.02 100	8.06 (100)	0.82 (100)	1.3 (100)	1.8 (100)	3.6 (100)
Haloperidol (1 mg/kg PO)	5.6 (93)	7.7 (96)	1.1 <sup>b</sup> (134)	1.5 <sup>b</sup> (115)	1.9 (106)	3.6 (100)
1192U90 (5 mg/kg PO)	6.6 (110)	8.2 (102)	1.1 <sup>b</sup> (134)	1.5 <sup>b</sup> (115)	2.1 <sup>b</sup> (117)	3.4 (94)
1192U90 (20 mg/kg PO)	5.9 (98)	8.1 (100)	1.5 <sup>b</sup> (183)	1.8 <sup>b</sup> (138)	2.3 <sup>b</sup> (128)	3.4 (94)

<sup>a</sup> Values in parenthesis represent % of control.

<sup>b</sup> Significantly different from control ( $p < 0.05$ ) by two-tailed  $t$  test.

**Figure 2.** Reversal by 1192U90 of *d*-amphetamine-induced inhibition of firing rate of substantia nigra (*open circles*) and ventral tegmental area (*solid circles*) dopamine neurons in rat. Details provided in the text.



negative extracellular action potentials of approximately 0.8- to 1.2-msec duration (Rogawski and Aghajanian 1981; VanderMaelen and Aghajanian 1983; Sprouse and Aghajanian 1987; Cox et al. 1993).

In experiments with IV drug injection, single-barrel glass electrodes were used to record unit activity. Stable baseline firing was recorded for 3 to 5 minutes before drug injection. Cumulative doses of 1192U90 (6.25–200 µg/kg) were injected every 60 seconds. The effect of 1192U90 on firing rate was determined by averaging the firing rate during the 60-sec interval after each dose and expressing it as a percentage of the baseline rate. Responses were averaged across doses and expressed as a mean  $\pm$  SEM.

In iontophoresis experiments, the central recording barrel of a five-barrel glass microelectrode was filled with 2 M NaCl containing 1% Pontamine sky blue dye (in vitro impedance 3–12 M $\Omega$ ). One side barrel was filled with 0.2 M NaCl and used for current balancing (in vitro impedance,  $\sim$ 20 M $\Omega$ ). Other barrels contained 1192U90 (1 mM, pH 3), the 5-HT<sub>1A</sub> agonist ( $\pm$ )8-OH-DPAT (20 mM, pH 5.5), or the 5-HT<sub>1A</sub> antagonist S(-)-propranolol (50 mM, pH 4.5). The in vitro impedance of drug-containing side barrels was between 60 and 110 M $\Omega$ . After baseline firing rates were recorded, ( $\pm$ )8-OH-DPAT was applied by iontophoresis (5- to 10-nA ejection currents) to ensure responsiveness to 5-HT<sub>1A</sub> stimulation. When the firing rate had returned to baseline values, 1192U90 was applied alone for 60-sec pulses and subsequently coapplied with S(-)-propranolol. Responses were determined by expressing mean firing rate during iontophoresis as a percentage of the firing rate preceding drug application. Responses were averaged across ejection currents and expressed as a mean  $\pm$  SEM.

## RESULTS

### Receptor Binding

1192U90 bound to D<sub>2</sub>/D<sub>3</sub>, 5-HT<sub>2</sub>, 5-HT<sub>1A</sub>,  $\alpha_1$  and  $\alpha_2$  receptors with high affinity (Table 2). The  $K_i$  values for 1192U90 at D<sub>2</sub>/D<sub>3</sub> and 5-HT<sub>2</sub> receptors indicated affinities about equal to those of risperidone and nine times greater than for clozapine. In addition, 1192U90 had high affinity at 5-HT<sub>1A</sub> receptors—about 100 and 500 times higher than risperidone and clozapine. Like risperidone, 1192U90 interacted with moderate affinity at D<sub>1</sub> receptors. 1192U90 showed only weak affinity at 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors, the sigma site, and the verapamil site of L-type calcium channels (Table 3). It was essentially inactive at 22 other sites (Table 3).

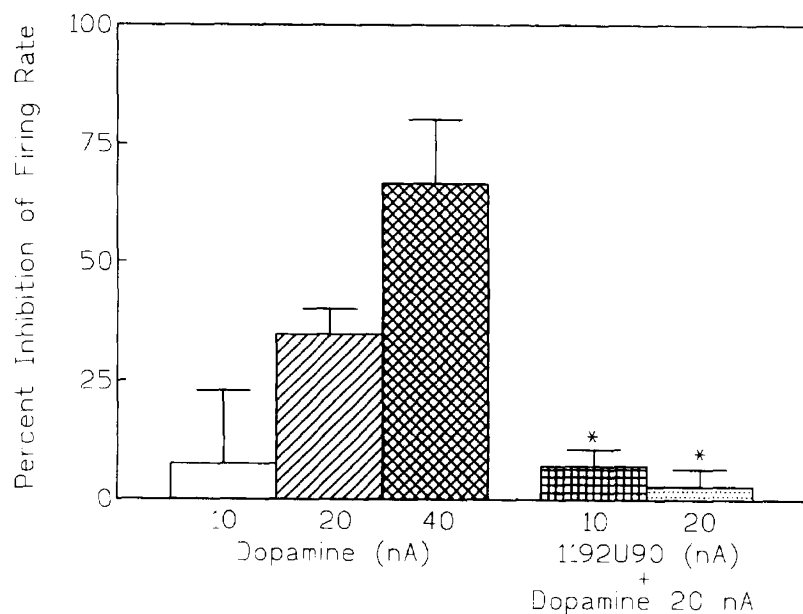
### Uptake

1192U90 inhibited somewhat the net uptake of <sup>3</sup>H-NE, <sup>3</sup>H-5-HT, and <sup>3</sup>H-DA in crude synaptosomes. The IC<sub>50</sub>s were 2.2 µM for NE, 2.4 µM for 5-HT, and 6.8 µM for DA uptake.

### Biogenic Amine Levels

Haloperidol 1 mg/kg PO significantly increased 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), the metabolites of DA ( $p \leq .05$  by two-tailed *t* test; Table 4). DOPAC was increased to 134% of control, HVA to 115%. NE, DA, 5-HT, and 5-hydroxyindolacetic acid (5-HIAA) were not significantly changed.

1192U90 5 mg/kg PO also significantly increased DOPAC and HVA, to 134% and 115%. The effects of 20 mg/kg were more pronounced: DOPAC to 183%, HVA



**Figure 3.** Effects of iontophoretically applied dopamine and 1192U90 on firing rate of SN and VTA dopamine neurons in rat. Application of dopamine with ejection currents of 10, 20, and 40 nA inhibited the firing rate of dopamine cells by  $7.4 \pm 15.4\%$  ( $n = 2$ ),  $34.8 \pm 5.3\%$  ( $n = 6$ ), and  $66.6 \pm 13.5\%$  ( $n = 3$ ), respectively. Simultaneous application of 1192U90 at 10 and 20 nA with dopamine (20 nA) limited the inhibition of dopamine cell firing rate to  $7.1 \pm 3.4\%$  ( $n = 2$ ) and  $2.8 \pm 3.6\%$  ( $n = 5$ ), respectively. \* $p < .05$  by  $t$  test, 1192U90 + dopamine versus dopamine alone.

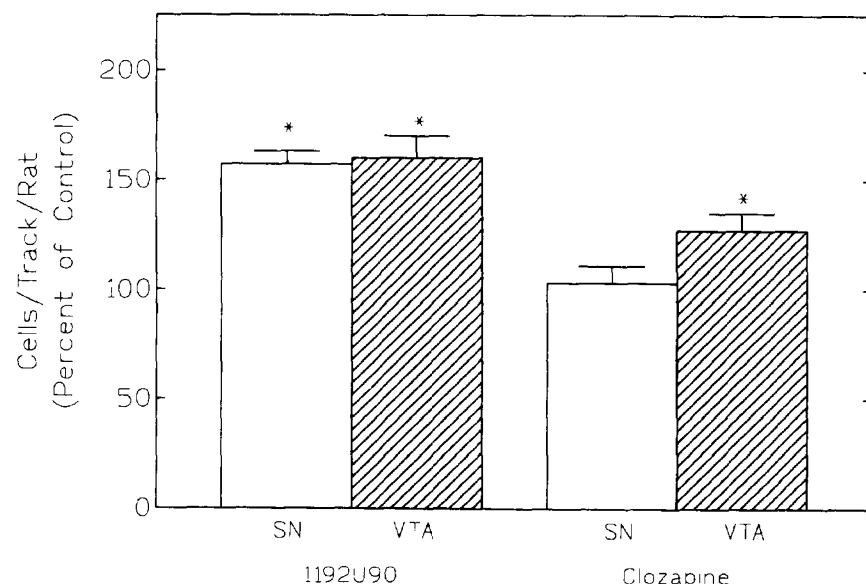
to 138%. Both doses significantly increased 5-HIAA, to 117% and 128%. NE, DA and 5-HT were not significantly changed.

**Dopamine Neurons: Antagonism of the Inhibitory Effects of Apomorphine and *d*-Amphetamine**

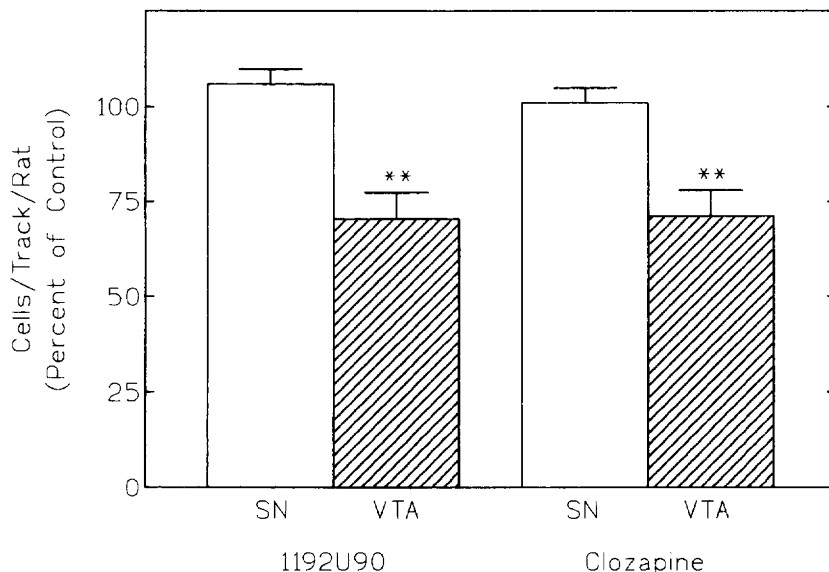
Apomorphine and *d*-amphetamine each inhibited dopamine cell firing rate, and the subsequent injection of 1192U90 reversed this inhibition (Figure 2). The average  $ED_{50}$  value for the reversal of apomorphine's effect by 1192U90 in SN and VTA was  $42 \mu\text{g}/\text{kg}$  ( $n = 7$ ). This value is comparable to an  $ED_{50}$  value of  $45 \mu\text{g}/\text{kg}$  for haloperidol in the same assay. 1192U90 reversed *d*-am-

phetamine-induced inhibitions with a mean  $ED_{50}$  value of  $11.3 \pm 2.8 \mu\text{g}/\text{kg}$  IV ( $n = 7$ , SN and VTA combined). Although only a small number of animals were tested, there was no apparent difference for the reversal of amphetamine-induced inhibitions of firing rates in SN ( $ED_{50}$   $14.3 \pm 6.7 \mu\text{g}/\text{kg}$  IV,  $n = 3$ ) and VTA ( $ED_{50}$   $9.0 + 1.7 \mu\text{g}/\text{kg}$  IV,  $n = 4$ ).

The effects of iontophoretically applied dopamine and 1192U90 were examined on dopamine neurons in the brains of six rats (Figure 3). Iontophoretic application of dopamine to spontaneously active cells inhibited neuronal firing rates. The simultaneous application of 1192U90 significantly limited the rate-inhibiting effect of dopamine. The baseline firing rates for these experi-



**Figure 4.** Effects of acute 1192U90 (0.8 mg/kg SC) and clozapine (20 mg/kg SC) on the number of spontaneously active SN and VTA dopamine neurons in rat 2 hours after injection. Both compounds increased the number in VTA. 1192U90 increased the number in SN, but clozapine did not. \* $p < .05$  versus control by ANOVA;  $n = 7-9$  rats/group.



**Figure 5.** Effects of chronic 1192U90 (0.8 mg/kg/day SC) and clozapine (20 mg/kg/day SC) on the number of spontaneously active dopamine neurons in rat after 28 daily injections. Both compounds decreased the number in VTA but not in SN. \*\**p* < .01 versus control by ANOVA; *n* = 7-10 rats/group.

ments were (in spikes/10 seconds): 54.3 ± 10.3 (DA 10 nA, *n* = 2), 44.5 ± 7.5 (DA 20 nA, *n* = 6), 38.0 ± 10.1 (DA 40 nA, *n* = 3), 61.3 ± 3.2 (DA 20 nA + 1192U90 10 nA, *n* = 2), and 44.9 ± 6.1 (DA 20 nA + 1192U90 20 nA, *n* = 5).

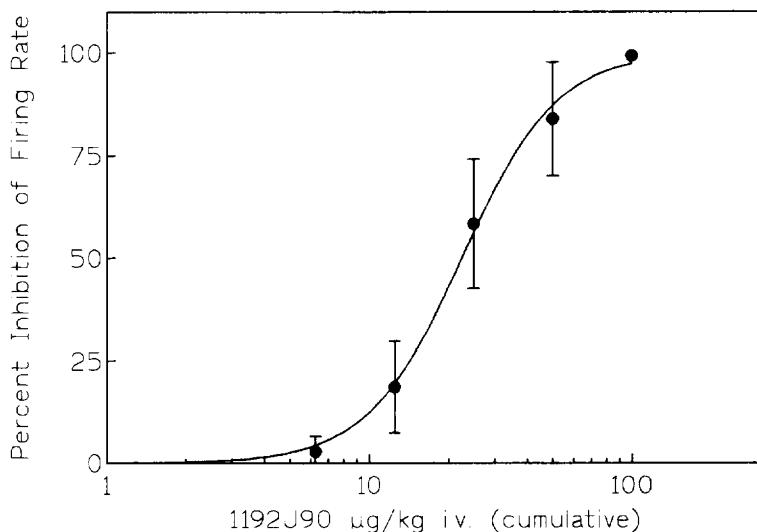
**Dopamine Neurons: Population Sampling after Acute and Chronic Administration of 1192U90 and Clozapine**

Figure 4 shows the effects of acute (2-hour) pretreatment with 1192U90 or clozapine on dopamine cell activity. After 1192U90, the number of spontaneously active dopamine neurons in VTA and SN increased by 60 ± 10% and 57 ± 6%, respectively, over vehicle control.

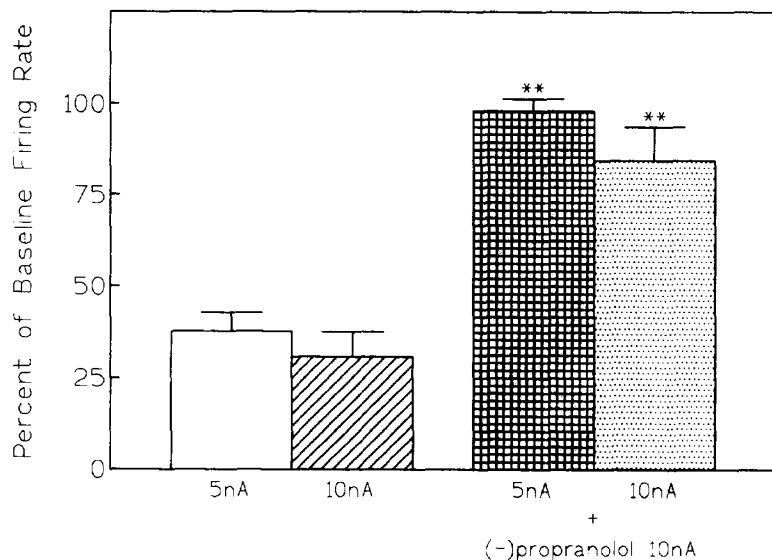
After clozapine, the number of spontaneously active dopamine cells in VTA increased by 27 ± 8%, but there was no change in SN activity (increased, 3 ± 8%). Mean spontaneous firing rates in both brain regions were unchanged 2 hours after either compound had been administered.

Figure 5 shows the effects of chronic dosing with 1192U90 or clozapine on dopamine cell activity. 1192U90 (0.8 mg/kg/day SC) decreased the number of spontaneously active dopamine neurons in VTA by 30 ± 7% but had no effect on the number of spontaneously active dopamine cells in SN (6 ± 7%). Clozapine (20 mg/kg/day SC) decreased the number of spontaneously active dopamine cells in VTA by 29 ± 8%, but had no effect on SN activity (increased, 1 ± 4%). Neither compound changed mean spontaneous firing rate.

**Figure 6.** Effect of systemic injection of 1192U90 on the firing rate of DRN serotonin neurons in rat. The ID<sub>50</sub> was 23 µg/kg. Each point represents the mean ± S.E.M. of five neurons.







**Figure 7.** Effect of iontophoretic application of 8-OH-DPAT on the firing rate of DRN neurons in rat. Application of 8-OH-DPAT (20 nM) with 5 and 10 nA ejection currents decreased the rate by 62.3% ± 5.1% (n = 14) and 69.2% ± 6.8% (n = 4), respectively. Simultaneous application of S(-)-propranolol (50 mM) with 10 nA current limited the effects of 8-OH-DPAT on the firing rate at 5 and 10 nA to 1.9 ± 3.3% (n = 7) and 15.5 ± 9.3% (n = 4), respectively. \*\* p < .01 by t test, 8-OH-DPAT alone versus 8-OH-DPAT + S(-)-propranolol.

**Serotonin Neurons: Effects of Acute 1192U90 on Dorsal Raphe Unit Activity**

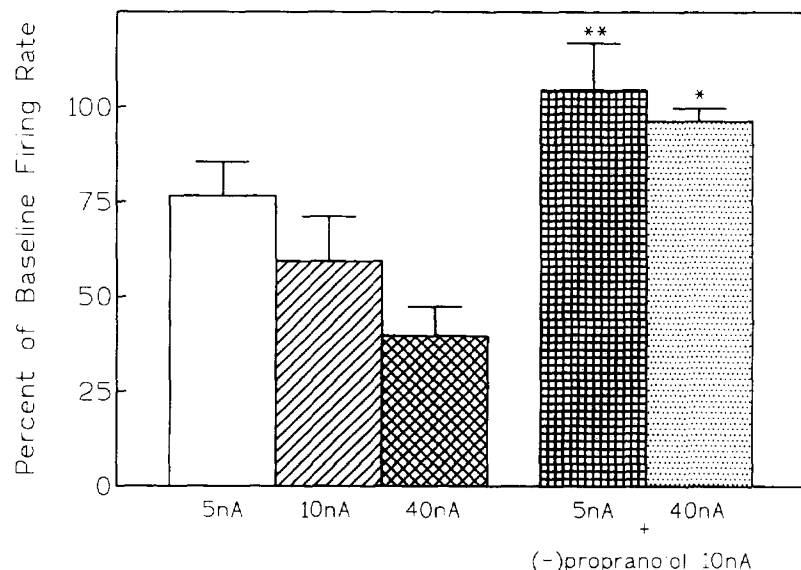
Systemic injection of 1192U90 (100 µg/kg IV cumulative) inhibited DRN cell firing rate by over 99%. The ID<sub>50</sub> value was 23 µg/kg (Figure 6).

Iontophoretic application of the 5-HT<sub>1A</sub> agonist (±)8-OH-DPAT inhibited DRN cell firing rate by 62.3 ± 5.1% and 69.2 ± 6.8% at ejection currents of 5 and 10 nA, respectively. Subsequent simultaneous iontophoresis of S(-)-propranolol at 10 nA on to the same neurons blocked the inhibition of firing exerted by (±)8OH-DPAT (Figure 7).

Iontophoretic application of 1192U90 at 5, 10, and 40 nA inhibited the DRN firing rate by 23.5% ± 9%, 40.6% ± 11.8%, and 60.2% ± 7.5%, respectively (Figure 8). Simultaneous application of S(-)-propranolol at 10 nA almost completely blocked the effects of 1192U90.

**DISCUSSION**

The discovery of the atypical antipsychotic clozapine was a major advance in neuropsychopharmacology. Clozapine was different from previous neuroleptics in that it was effective against both positive and negative symptoms of schizophrenia (Kane et al. 1988; Meltzer et al. 1989; Lieberman 1993), and it caused fewer extrapyramidal side effects (Gerlach et al. 1974; Shopsin et al. 1979; Claghorn et al. 1987; Casey 1989). However, its association with agranulocytosis has limited its clinical usefulness (Idänpään-Heikkilä et al. 1975; Griffith and Saameli 1975; Lieberman et al. 1988). Because clozapine has several sites of action, there are many theories as to which neurochemical attributes are responsible and necessary for its atypical control of schizophrenia (Meltzer 1991).



**Figure 8.** Effect of iontophoretic application of 1192U90 on the firing rate of DRN neurons in rat. Application of 1192U90 (1 mM) with 5, 10, and 40 nA ejection currents decreased the rate by 23.5% ± 9% (n = 4), 40.6% ± 11.8% (n = 3), and 60.2% ± 7.5% (n = 5), respectively. Simultaneous application of S(-)-propranolol (50 nM) with 10 nA current increased the rate by 4.5% ± 12.5% at 5 nA (n = 2) and decreased the rate by 3.6% ± 3.4% at 40 nA (n = 4). \*p < 0.5, \*\*p < .01, by t test, 1192U90 alone versus 1192U90 + S(-)-propranolol.

Possibly the most widely accepted theory on the neurochemical basis of schizophrenia is that hyperactivity of DA systems in the brain is at least partially responsible for psychosis (Andreasen 1988; Sunahara et al. 1993). Although there is little evidence for D<sub>1</sub> receptor blockade explaining the mechanism of antipsychotic activity, D<sub>2</sub> (and/or D<sub>3</sub>) receptor antagonism is clearly implicated (Sunahara et al. 1993). Sunahara et al. (1993), point out that "clinically effective free drug concentrations of virtually all the antipsychotics correlate well with their ability to inhibit [<sup>3</sup>H]-spiperone binding to the D<sub>2</sub> dopamine receptor." Specifically, D<sub>2</sub> receptor blockade in the limbic system seems to be important in controlling psychosis, whereas D<sub>2</sub> receptor blockade in the nigrostriatal system seems to be related to extrapyramidal side effects (Bunney 1992; Schotte et al. 1993). 1192U90, like clozapine and risperidone, binds to D<sub>2</sub> receptors with high affinity. The reversal of apomorphine- and *d*-amphetamine-induced inhibition of SN and VTA dopamine neuron firing rates by low doses of 1192U90 indicates that this compound is a potent antagonist of the dopamine receptor (or receptors) that mediates that effect (Bunney et al. 1973). Dopamine agonists act on somatodendritic D<sub>2</sub> or D<sub>3</sub> autoreceptors and inhibit the firing rates of neurons in the SN and VTA (Bunney and Aghajanian 1978; White and Wang 1984; Liu et al. 1994), whereas dopamine antagonists block or reverse this action (Bunney et al. 1973).

Acute doses of 1192U90 (0.8 mg/kg SC, 2 hours before sampling) resulted in an increased number of spontaneously active SN and VTA dopamine neurons. In our hands, clozapine (20 mg/kg SC, 2 hour presampling) had no effect on spontaneous activity of dopamine neurons in either region. The reason for this difference cannot be ascertained from the present data. Clozapine and 1192U90 clearly have different patterns of receptor binding, a factor that could underlie the differences in acute activity. This finding should not negate the potential atypical nature of 1192U90. In fact, the acute effects of clozapine itself are not uniform across laboratories. For instance, Chiodo and Bunney (1985) reported that clozapine (20 mg/kg PO, 1-hour presampling) produced substantial increases in the number of active dopamine cells in both the SN and the VTA. On the other hand, White and Wang (1983) observed a selective increase in VTA activity and no effect on A9 activity after clozapine administration (20 mg/kg SC, 2 hours presampling).

Chronic dosing with antipsychotic drugs produces a time-dependent inactivation of dopamine cell activity in the VTA and/or SN of rats (Chiodo and Bunney 1983; White and Wang 1983a,b). It has been suggested that inhibition of spontaneous dopamine cell activity in the VTA is related to the efficacy of these compounds as antipsychotics, whereas inactivation of SN dopamine neurons is related to the occurrence of extrapyramidal

side-effects such as tardive dyskinesia. Most atypical antipsychotics preferentially decrease VTA activity without significantly altering spontaneous SN activity (Chiodo and Bunney 1983; White and Wang 1983b). 1192U90, like clozapine, displays this profile and may also be an atypical antipsychotic when introduced into the clinic. Very recently, the depolarization inactivation model of antipsychotic effect has come under criticism because of apparent inconsistencies with biochemical data, wide variability from study to study, and different effects when experiments are performed in awake versus anesthetized rats (Mereu et al. 1995). It has been suggested that the depolarization inactivation of dopaminergic neurons after chronic neuroleptics is an artifact secondary to a combined effect of the antipsychotic plus general anesthesia (Mereu et al. 1995). The findings underlying that suggestion (Mereu et al. 1995) do not agree, however, with those of Bunney and Grace (1978), who found depolarization inactivation in both chloral hydrate-anesthetized rats and unanesthetized rats. In our opinion, the model continues to have general predictive value for the nature of antipsychotic compounds in that chronic dosing of most, if not all antipsychotic drugs results in depolarization inactivation of VTA neurons in anesthetized rats, atypical antipsychotic drugs result in preferential inactivation of VTA versus SN dopamine neurons, and D<sub>2</sub> antagonists that are not antipsychotic (e.g., metoclopramide) do not result in depolarization inactivation (White and Wang 1983a,b).

Considerable attention has recently been placed on the dopamine D<sub>4</sub> receptor subtype (Van Tol et al. 1991). Clozapine has been reported to have selectivity for this site over the dopamine D<sub>2</sub> subtype (Seeman 1992; Lahti et al. 1993), although other investigators have demonstrated that this apparent selectivity may be due to the assay method used to define the affinity to the dopamine D<sub>2</sub> receptor subtype (Malmberg et al. 1993; Durcan et al. 1995). In parallel experiments using <sup>3</sup>H-spiperone to assess affinities at D<sub>2</sub> and D<sub>4</sub> receptors Durcan et al. (1995) found that 1192U90, like clozapine, was selective for D<sub>4</sub> receptors over D<sub>2</sub> with K<sub>d</sub> values of 0.21 versus 0.12 nM, respectively. Neither clozapine nor 1192U90 were selective if <sup>3</sup>H-raclopride was used to determine affinity at D<sub>2</sub> receptors. Thus, it currently remains uncertain which receptor subtype, if either, underlies the antipsychotic efficacy of clozapine.

Another theory on the mechanism of atypical antipsychotics that has come from studying clozapine's unique profile proposes that a balance of 5-HT<sub>2</sub> and D<sub>2</sub> antagonism is responsible for atypical antipsychotic activity and reduced side effect profiles (Meltzer 1991). Studies in this vein have indicated that higher occupancy of 5-HT<sub>2</sub> receptors relative to D<sub>2</sub> receptors may be responsible for reduced incidence of extrapyramidal side effects (Schotte et al. 1993; Stockmeier et al. 1993).

1192U90, like clozapine and risperidone, has a 10-fold higher affinity for 5-HT<sub>2</sub> than for D<sub>2</sub>. This could lead to higher occupancy of 5-HT<sub>2</sub> receptors than D<sub>2</sub> receptors. A potential for reduced side effect liability with 1192U90 is further suggested by its weakness in antagonizing apomorphine-induced stereotypy and catalepsy (Rigdon et al. 1996).

The dose-related inhibition of DRN firing after IV injections of 1192U90 suggests that it is a 5-HT<sub>1A</sub> agonist. 1192U90, with an ID<sub>50</sub> of 23 µg/kg, is less potent than the 5-HT<sub>1A</sub> agonist (±)8-OH-DPAT (ID<sub>50</sub> = 1.5 µg/kg; Cox et al. 1993) but similar in potency to ipsapirone (Sprouse and Aghajanian 1987; Cox et al. 1993), a 5-HT<sub>1A</sub> receptor ligand with anxiolytic properties (Traber and Glaser 1987).

Direct application of 1192U90 by microiontophoresis also decreased DRN cell firing rate, an effect that may be mediated by direct stimulation of 5-HT<sub>1A</sub> autoreceptors on DRN cell bodies and dendrites. Although 1192U90 is a weak inhibitor of serotonin uptake (IC<sub>50</sub> = 2.5 µM), pharmacokinetic studies performed with dosing schemes identical to those of the electrophysiological experiments produced brain levels of 1192U90 that were 1,000 times lower than the *in vitro* IC<sub>50</sub> for inhibition of serotonin uptake (K. M. Hedeem, personal communication). This would indicate that the effect of 1192U90 on DRN firing rate is not due to inhibition of uptake, but is, rather, a direct action. The inhibition of DRN firing rate by 1192U90 or (±)8-OH-DPAT was blocked by simultaneous iontophoretic application of S(-)-propranolol, a 5-HT<sub>1A</sub> antagonist, confirming that the effect was mediated to a major extent by 5-HT<sub>1A</sub> receptors (Sprouse and Aghajanian 1986). Other antipsychotic drugs such as methiothepin, clozapine, and thioridazine also inhibit DRN firing rate; however, their effects correlate with their affinities at α<sub>1</sub> receptors (Gallagher and Aghajanian 1976). Our results do not rule out some contribution from α<sub>1</sub> blockade to the inhibition of DRN firing rate by 1192U90; nevertheless, antagonism of the inhibition by iontophoretically applied S(-)-propranolol supports the conclusion that the effect of 1192U90 is primarily due to 5-HT<sub>1A</sub> stimulation.

The clinical relevance of an antipsychotic drug with 5-HT<sub>1A</sub> agonist activity is not known, but this property may confer positive attributes. Compounds with 5-HT<sub>1A</sub> agonist or partial agonist effects include buspirone, ipsapirone, and gepirone, which are anxiolytic (Traber and Glaser 1987). The results of animal behavioral tests by Rigdon et al. (1996) suggest an anxiolytic potential for 1192U90. Anxiety is often a component of schizophrenia; therefore, coincident anxiolytic activity in an antipsychotic drug would be very desirable. In addition to potential anxiolytic effect, agonist activity at 5-HT<sub>1A</sub> receptors might also contribute to the "atypical" antipsychotic profile of 1192U90. There have been previous attempts to design compounds possessing D<sub>2</sub> antago-

nism and 5-HT<sub>1A</sub> agonism with the hope of developing an atypical antipsychotic (Lowe et al. 1991). A rationale for such a combination of activities is based on the observation that buspirone, ipsapirone, and (±)8-OH-DPAT reverse haloperidol-induced catalepsy (McMillen et al. 1988; Hicks 1990). Furthermore, (±)8-OH-DPAT suppresses conditioned avoidance behavior and selectively decreases limbic dopamine synthesis (Ahlenius 1989).

1192U90, like clozapine, risperidone, and many other antipsychotic drugs, has high affinity for the α<sub>1</sub> receptor. Because of this high affinity for the α<sub>1</sub> receptor, it has been proposed that α<sub>1</sub> blockade may be a component for antipsychotic activity (Cohen and Lipinski 1986; Baldessarini et al. 1992; Sleight et al. 1993) and may mediate differential effects on SN and VTA dopamine neurons after chronic dosing (Chiodo and Bunney 1983). Cohen and Lipinski (1986) demonstrated that, following chronic treatment with clozapine, thioridazine, chlorpromazine, fluphenazine, or haloperidol, α<sub>1</sub> receptors were upregulated, indicating a physiologically significant *in vivo* blockade of these receptors. In contrast, D<sub>2</sub> receptor upregulation occurred only after chronic fluphenazine or haloperidol. This suggests that α<sub>1</sub> receptor blockade may be involved in the mechanism of therapeutic effect of antipsychotic drugs (Cohen and Lipinski 1986). Electrophysiological studies add evidence for a noradrenergic role in the modulation of dopamine neuron activity in the VTA (Chiodo and Bunney 1983; Grenhoff and Svensson 1994; Andersson et al. 1994). However, it is difficult to ascribe the atypical nature of some antipsychotics to α<sub>1</sub> antagonism because haloperidol, which is not atypical, is nearly equipotent at this receptor compared to clozapine (Hacksell et al. 1995). A recent review of the preclinical effects of antipsychotic compounds concluded that there is no evidence that α<sub>1</sub> blockade is a positive attribute in an antipsychotic drug (Jackson et al. 1994).

It is well established that administration of antipsychotic drugs increase the level of DA metabolites in brain (Carlsson and Lindqvist 1963; Bunney et al. 1973; Bürki et al. 1975; Coward 1992). This reflects an increase in DA turnover. Typical antipsychotic drugs like haloperidol increase DA turnover by activating feedback systems to presynaptic dopamine neurons following DA receptor blockade (Bürki et al. 1974, 1975). Clozapine increases both DA and metabolite levels in the striatum by increasing DA release in response to D<sub>1</sub> receptor blockade but not D<sub>2</sub> blockade (Imperato and Angelucci, 1988; Coward 1992). Acute administration of 1192U90 (5 and 20 mg/kg PO) increased levels of DOPAC and HVA as well as 5HIAA, maybe because of its interaction with 5-HT receptors. These effects are probably due to receptor blockade because these doses of 1192U90 yield brain levels that are about 100-fold lower than the IC<sub>50</sub> values for inhibition of uptake of dopa-

mine or serotonin (K. M. Hedeén, personal communication).

It remains to be determined which neurochemical characteristics are necessary to obtain good antipsychotic activity with minimal side effects. 1192U90, like most new antipsychotic compounds, has high affinity for D<sub>2</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>2</sub>, and α<sub>1</sub> receptors. Our in vivo single-unit recordings indicate that 1192U90 is a potent dopamine D<sub>2</sub>/D<sub>3</sub> antagonist as well as a 5-HT<sub>1A</sub> agonist. Population sampling of SN and VTA dopamine neuronal activity show that chronically administered 1192U90 selectively decreases the activity of VTA dopamine neurons that are associated with limbic projections. These properties, taken together with behavioral data, lead us to propose that 1192U90 will have an atypical antipsychotic profile in the clinic.

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