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Effects of Amperozide on Psychostimulant-Induced Hyperlocomotion and Dopamine Release in the Nucleus Accumbens

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KIMURA, K., G. G. NOMIKOS AND T. H. SVENSSON. *Effects of amperozide on psychostimulant-induced hyperlocomotion and dopamine release in the nucleus accumbens.* PHARMACOL BIOCHEM BEHAV 44(1) 27-36, 1993.—*N*-Ethyl-4-[4′,4′-bis(*p*-fluorophenyl)-butyl]-1-piperazine carboxamide [amperozide (APZ)] is a novel atypical neuroleptic that appears to selectively act on the limbic system. The present study investigated behavioral and biochemical effects of APZ on either *d*-amphetamine (AMPH)- or cocaine (COC)-treated rats. Behavior was assessed by locomotor activity measurements. Compared to saline controls, APZ (5 and 10 mg/kg, SC) decreased spontaneous locomotion. AMPH (1.0 mg/kg, SC)- or COC (10 mg/kg, IP)-induced hyperlocomotion was markedly reduced by APZ administered 20 min earlier. Biochemical data were obtained by in vivo microdialysis in freely moving animals. APZ dose dependently increased interstitial concentrations of dopamine (DA, +25%) and its metabolite, homovanillic acid (HVA, +20%), in the nucleus accumbens (NAC). While either AMPH or COC alone increased DA levels (450 and 270%, respectively), pretreatment with APZ had no effect on these increases. In contrast, APZ pretreatment dose dependently attenuated the reduction of DA metabolites induced by both AMPH and COC. Thus, APZ blocked hyperlocomotion induced by psychostimulants without producing correlative changes in DA concentrations in the NAC.

Amperozide Locomotor activity Amphetamine Cocaine Microdialysis Nucleus accumbens Rat

N-Ethyl-4-[4′,4′-bis(*p*-fluorophenyl)-butyl]-1-piperazine carboxamide [amperozide (APZ)] is a novel atypical neuroleptic characterized by high affinity for serotonin [5-hydroxytryptamine$_2$ (5-HT$_2$) receptors, moderate affinity for α_1-adrenergic receptors, and weak affinity for D_2 dopamine receptors (25,40,63). There is accumulating evidence that APZ acts preferentially on the limbic system. APZ is reported to influence some behaviors related to emotion and mood. For example, APZ increases motivation in a behavioral despair test and reduces aggressive behavior in rats (24). In electrophysiological experiments, APZ exerts selective actions on dopamine (DA) cells projecting from ventral tegmental area (VTA) (22). Further, APZ slightly increases DA synthesis and turnover in limbic areas but not in the striatum (50).

APZ has been shown to antagonize amphetamine (AMPH)-induced hyperlocomotion in mice (14,23) and rats (68). It is well established that the hypermotility induced by psychostimulants is largely mediated by enhanced dopaminergic transmission in the brain (15,19,35,39,60,64). Administration of AMPH or cocaine (COC) increases DA concentration in the striatum and nucleus accumbens (NAC), as measured by microdialysis (5,7,9,12,26-28,34,36,41,46,71). Classic neuroleptics are characterized by their antagonism of hypermotility and stereotypy produced by psychostimulants (1,15,48,60, 64). These behavioral effects are presumably mediated by DA receptor blockade. However, the effects of APZ on AMPH-induced hyperlocomotion cannot be solely attributed to DA receptor antagonism because APZ shows only weak affinity for DA receptors in vitro.

In vitro studies have indicated that APZ increases basal DA overflow and inhibits AMPH-induced DA release in striatal and limbic tissue slices (17,18). A recent in vivo microdialysis study showed that APZ increased basal DA concentrations from rat striatum and NAC (29). Further, APZ was found to attenuate AMPH-induced DA release in both brain regions (29). These effects were attributed to presynaptic ac-

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tion of APZ on DA release and uptake. Some supporting evidence is provided by in vitro studies that show APZ is a moderately effective DA uptake inhibitor (17,18). An additional explanation may be provided by the action of APZ on serotonergic systems, as APZ has been shown to possess potent affinity for 5-HT_2 receptors, as well as for 5-HT uptake sites (17).

To further investigate the effects of APZ on behavior in relation to DA release in the NAC, open-field and in vivo microdialysis techniques were combined in this study. Open-field measurements were used to study the effects of APZ on spontaneous motor activity and hyperlocomotion induced by AMPH and COC. In vivo microdialysis was employed to assess the effects of APZ on basal DA release in the NAC, as well as on AMPH- and COC-induced DA release in awake, freely moving animals. The same time course in drug administration for both locomotor activity and microdialysis experiments was maintained to obtain comparable results from both behavioral and biochemical data.

METHOD

Animals

Male Wistar rats weighing 250–350 g were used. Rats were housed under standard laboratory conditions and maintained on a 12 L : 12 D cycle (lights on at 0600 h), with ad lib access to food and water.

Behavioral Study

Locomotor activity was measured by computer-assisted photocell equipment boxes as described previously (16). Animals were placed individually in a square open-field arena (680 × 680 × 450 mm) within the apparatus, which was lined with two rows of photocells on each wall. The apparatus was ventilated, sound-attenuated, and kept dark during experimental sessions. Movement of the animal resulted in interruption of photobeams, which were collected and counted by a microcomputer. Computer recordings of measured horizontal activity, forward locomotion, rearing, and corner time were taken. Horizontal activity was counted as all photobeam interruptions in the lower rows. Of these, successive interruptions in the same direction were registered as forward locomotion. All photobeam interruptions in the upper rows were registered as rearing. Corner time was total duration of photobeam interruptions in the four corners.

Only experimentally naive rats were used. Animals arrived at least 1 week before use and were housed six to a cage. On the day of experiment, rats were brought to the behavioral room in the home cage and allowed to become accustomed to the new room for 60 min. Rats were first injected SC with saline or APZ and then placed in a clean holding cage. Twenty minutes later, rats received the second injection (saline SC, AMPH SC, saline IP, COC IP; depending upon treatment) and were immediately placed in the locomotor activity boxes.

Each experimental session lasted 40 min. The photocell boxes were wiped clean after each session. Behavioral experiments were conducted during the day between 0900 and 1700 h.

Surgery and Microdialysis

Rats were anesthetized with barbiturates (Mebumal 60 mg/kg, IP) and mounted on a stereotaxic apparatus. Vertical probes of the concentric type were stereotaxically implanted in the NAC. Coordinates were AP +3.6, ML −1.4, DV −8.2 relative to bregma (49). Dialysis occurred through a 2.25-mm semipermeable membrane (copolymer of acrylonitrile and sodium methallyl sulfonate, I.D. = 0.24 mm, 40,000 Da, AN 69 Hospal).

After surgery, rats were housed individually in Plexiglas cages (32 × 35 × 50 cm) and given free access to food and water. All experiments were performed approximately 48 h postsurgery in awake, freely moving animals during the light cycle. After a stable baseline was established, each rat received either saline or drug (APZ, AMPH, or COC). In some experiments, AMPH or COC was injected 20 min after APZ.

Microdialysis was performed using automated on-line sampling (45). The dialysis probe was perfused with perfusion solution (147 mM NaCl, 3.0 mM KCl, 1.3 mM $CaCl_2$, 1.0 mM $MgCl_2$, and 1.0 mM sodium phosphate, pH 7.4) at a rate of 2.5 μl/min set by a microinfusion pump (Harvard Apparatus, South Natick, MA). The perfusate was loaded directly into the sample loop of the injector (Valco, Houston, TX) and automatically injected into the analytic system every 20 min. An adjustable timer (DVSP, Valco) controlled the loading and injection modes of the injector. Upon completion of the experiments, animals were sacrificed and brains preserved in 5% formalin. Each brain was sliced on a microtome (50μm), stained (Nissl), and examined under microscope for probe placement. Only rats with probes verified to be located in the NAC were included in the study.

Biochemical Assay

Concentrations of DA, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) were determined by high-performance liquid chromatography with electrochemical detection (HPLC-ED) as described previously (45). Separation of DA and the acid metabolites was achieved by reverse-phase liquid chromatography (150 × 4.6 mm, Nucleosil 5 μm, C18) with mobile phase consisting of 0.055 M sodium acetate with 0.1 mM octanesulfonic acid, 0.01 mM Na_2EDTA, and 10% methanol (pH = 4.1, adjusted with glacial acetic acid). The mobile phase was delivered by an HPLC pump (LKB, Bromma, Sweden; 2150) at 0.8 ml/min. Chromatograms were recorded on a two-pen chart recorder (Kipp & Zonnen, Delft, Holland; BD41).

Drug Treatment

All drugs were dissolved in saline (0.9% NaCl). Amperozide (Pharmacia LEO Therapeutics AB, Malmö, Sweden) was administered SC in doses of 5 or 10 mg/kg. *d*-Amphetamine sulfate (Sigma Chemical Co., St. Louis, MO, USA) was also given SC (1.0 mg/kg) and cocaine HCl (Apoteksbolaget, Stockholm, Sweden) was administered IP (10 mg/kg). Control animals received saline SC or IP, injected in a volume of 1.0 ml/kg.

Data Analysis

For the purposes of graphic representation, the average of three baseline samples immediately preceding the last baseline sample before the saline or drug injection was defined as 100%. All subsequent measures were related to these values, and the mean percentages were calculated for each 20-min sample across rats in all groups. For statistical evaluation of the data, the percent changes were used. Data were analyzed by one- and two-way (treatment × time) analysis of variance

(ANOVA) with repeated measures, followed by the Newman-Keuls test for multiple comparisons with a criterion of $p < 0.05$.

For the behavioral data, raw values of 40-min recording of behavioral measures were used. Data were analyzed by the two-way ANOVA, followed by planned comparisons using pooled t-tests. A p value less than 0.05 was considered significant.

RESULTS

Effect of APZ on AMPH- and COC-Induced Hyperlocomotion

Compared to saline, APZ had significant effects on open-field activity measurements (Tables 1 and 2). The effects of APZ were more pronounced in groups that received saline IP as the second injection (Table 2). Both doses of APZ had significant effects on horizontal activity [APZ 5 mg/kg ($t = 3.83$, $p < 0.001$); APZ 10 mg/kg ($t = 4.79$, $p = 0.0001$)], forward locomotion [APZ 5 mg/kg ($t = 3.06$, $p = 0.0039$); APZ 10 mg/kg ($t = 3.845$, $p < 0.001$)], and rearing [APZ 5 mg/kg ($t = 6.65$, $p < 0.001$); APZ 10 mg/kg ($t = 7.05$, $p < 0.001$)]. Corner time was significant only for APZ 10 mg/kg ($t = 2.53$, $p = 0.0141$).

Compared to animals that received saline SC as the second injection, the higher dose of APZ significantly reduced horizontal activity ($t = 2.68$, $p = 0.0099$) and forward locomotion ($t = 2.62$, $p = 0.0114$). Neither horizontal activity nor forward locomotion were influenced by APZ 5 mg/kg. Both doses of APZ significantly decreased rearing [APZ 5 mg/kg ($t = 2.55$, $p = 0.0134$); APZ 10 mg/kg ($t = 2.97$, $p = 0.0049$)]. There were no significant differences in corner time at any dose.

There were significant differences between saline- and AMPH-treated rats. AMPH significantly increased horizontal activity ($t = 3.82$, $p < 0.001$) and forward locomotion ($t = 2.59$, $p = 0.0121$), whereas it reduced corner time ($t = 2.13$, $p = 0.0359$). APZ antagonized these behavioral effects of AMPH. Pretreatment with either dose of APZ significantly reduced horizontal activity in AMPH-treated rats ($t = 2.791$, $p = 0.0075$; $t = 3.062$, $p = 0.0039$, for the 5- and 10-mg/kg doses of APZ, respectively) and forward locomotion ($t = 2.584$, $p = 0.0121$; $t = 3.951$, $p < 0.001$, for the 5- and 10-mg/kg doses of APZ, respectively). While raw values for corner time showed large percent changes after APZ pretreatment, they were not statistically different compared to controls owing to wide variability of the data. For the same reasons, there was no significant difference in rearing between saline and AMPH groups (Table 1).

There were significant differences between saline- and COC-treated rats in all four behavioral measures: horizontal activity ($t = 8.15$, $p < 0.001$), forward locomotion ($t = 5.91$, $p < 0.001$), corner time ($t = 4.15$, $p < 0.001$), and rearing ($t = 9.80$, $p < 0.001$). Pretreatment with APZ resulted in significant differences in COC-treated rats in all behavioral measures except corner time between saline and APZ 5-mg/kg groups (Table 2).

When locomotor activity was calculated as percent changes, APZ pretreatment had similar effects in AMPH and COC groups as in saline groups. The most robust effect was seen in corner time. There was a 4.5- to 6.5-fold increase with pretreatment of APZ 5 mg/kg and an 8-fold increase with pretreatment of APZ 10 mg/kg. In comparison, in saline rats the maximal increase was 70%.

Effect of APZ on Dialysate Concentrations of DA, Its Metabolites, and 5-HIAA From the NAC

There was no difference in mean values of basal DA and its metabolites among the treatment groups: DA, $F(2, 14) = 0.023$; DOPAC, $F(2, 14) = 1.26$; HVA, $F(2, 14) = 0.019$; 5-HIAA, $F(2, 14) = 0.025$.

APZ exerted a dose-dependent increase in DA concentration. Although there was no difference in DA concentrations between saline and APZ 5 mg/kg, $F(1, 9) = 0.28$, there was a significant increase with APZ 10 mg/kg, $F(1, 10) = 18.48$, $p < 0.001$. Overall ANOVA showed that all effects were sig-

TABLE 1

EFFECTS OF AMPEROZIDE ON AMPHETAMINE-INDUCED LOCOMOTOR ACTIVITY

Treatment	Horizontal Activity	Forward Locomotion	Corner Time	Rearing
SAL + SAL	1,504 ± 167	379 ± 52	759 ± 247	256 ± 43
APZ 5 + SAL	919 ± 149 (−39%)	175 ± 55 (−54%)	1,076 ± 321 (+42%)	59 ± 22* (−77%)
APZ 10 + SAL	523 ± 102* (−65%)	68 ± 28* (−82%)	1,292 ± 327 (+70%)	27 ± 11* −89%)
SAL + AMPH	2,987 ± 330*	687 ± 96*	52 ± 17*	396 ± 115
APZ 5 + AMPH	1,929 ± 392† (−35%)	379 ± 139† (−45%)	284 ± 138 (+446%)	152 ± 38† (−62%)
APZ 10 + AMPH	1,826 ± 316† (−39%)	218 ± 85† (−68%)	475 ± 150 (+813%)	128 ± 29† (−68%)

Activity scores measured for 40 min for each treatment group are expressed as mean ± SEM ($n = 9$ in all groups). Animals were first injected SC with saline or amperozide (5 or 10 mg/kg); 20 min later, they received SC saline or amphetamine (1.0 mg/kg). Percent changes were calculated using saline or amphetamine scores as baseline.

*$p < 0.05$ compared to saline.

†$p < 0.05$ compared to amphetamine.

TABLE 2

EFFECTS OF AMPEROZIDE ON COCAINE-INDUCED LOCOMOTOR ACTIVITY

Treatment	Horizontal Activity	Forward Locomotion	Corner Time	Rearing
SAL + SAL	1,575 ± 139	378 ± 43	1,241 ± 129	289 ± 43
APZ 5 + SAL	644 ± 84* (−59%)	116 ± 21* (−69%)	1,513 ± 238 (+22%)	32 ± 10* (−89%)
APZ 10 + SAL	374 ± 42* (−76%)	39 ± 12* (−90%)	1,950 ± 253* (+57%)	7.6 ± 2.2* (−97%)
SAL + COC	3,558 ± 342*	882 ± 126*	113 ± 22*	669 ± 47*
APZ 5 + COC	936 ± 139† (−74%)	155 ± 40† (−82%)	856 ± 171† (+658%)	45 ± 11† (−93%)
APZ 10 + COC	959 ± 80† (−73%)	108 ± 41† (−88%)	1,022 ± 268† (+804%)	51 ± 15† (−92%)

Activity scores measured for 40 min for each treatment group are expressed as mean ± SEM (n = 8–10 in all groups). Animals were first injected SC with saline or amperozide (5 or 10 mg/kg); 20 min later, they received IP saline or cocaine (10 mg/kg). Percent changes were calculated using saline or cocaine scores as baseline.

*$p < 0.05$ compared to saline.

†$p < 0.05$ compared to cocaine.

nificant: treatment, $F(2, 14) = 10.59$, $p < 0.001$, time, $F(9, 126) = 2.08$, $p = 0.04$, and treatment × time, $F(18, 126) = 2.07$, $p = 0.01$. Posthoc comparisons showed statistically significant increases in seven data points (Fig. 1).

There was a slight increase in DOPAC levels after APZ 10 mg/kg administration. However, neither treatment nor treatment × time interaction effects reached significance. Only time, $F(9, 126) = 2.30$, $p = 0.02$, effect was significant (Fig. 2).

HVA output increased after administration of both doses of APZ. All effects were significant: treatment, $F(2, 14) = 8.82$, $p < 0.001$, time, $F(9, 126) = 7.29$, $p < 0.001$, and treatment × time, $F(18, 126) = 5.49$, $p < 0.001$. Posthoc analysis showed significant ($p < 0.05$) effects with APZ 10 mg/kg at 60–180 min, whereas APZ 5 mg/kg significantly increased HVA at 120–180 min (Fig. 2).

5-HIAA output also increased after APZ injection irrespective of dose. All effects were significant: treatment, $F(2, 14) = 5.91$, $p = 0.01$, time, $F(9, 126) = 6.15$, $p < 0.001$, and treatment × time, $F(18, 126) = 2.92$, $p < 0.001$. Posthoc comparisons showed significant ($p < 0.05$) increases with APZ 10 mg/kg starting at 80 min and APZ 5 mg/kg starting at 100 min; these effects lasted throughout the experiment (Fig. 2).

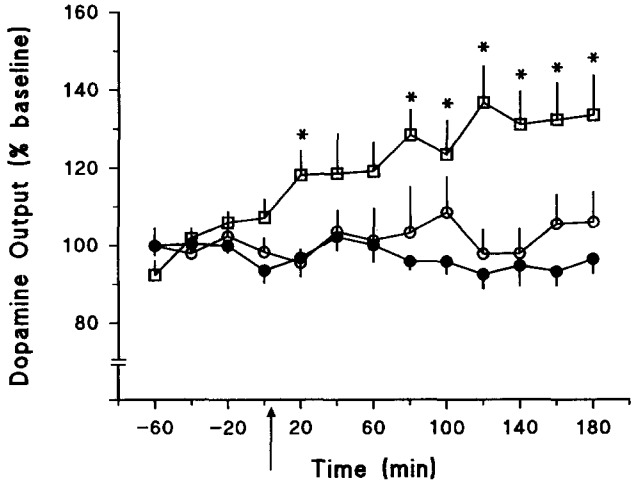

FIG. 1. Effect of amperozide (APZ) (5 mg/kg, SC, ○, n = 5; 10 mg/kg, SC, □, n = 6) or saline (1 ml/kg, SC, ●, n = 6) on dialysate concentrations of dopamine (DA) from nucleus accumbens. Each point represents the mean percent change of baseline. The overall mean ± SEM basal value of DA was 2.61 ± 0.27 fmol/min (n = 17). The arrow indicates injection of drug or vehicle. *$p < 0.05$ APZ 10 compared to saline.

Effect of APZ on AMPH-Induced Changes of Dialysate Concentrations of DA, Its Metabolites, and 5-HIAA From the NAC

There was no difference in mean values of basal DA and its metabolites among the treatment groups: DA, $F(2, 15) = 0.77$; DOPAC, $F(2, 15) = 0.33$; HVA, $F(2, 15) = 0.38$; 5-HIAA, $F(2, 15) = 1.94$.

Administration of AMPH increased DA concentrations to approximately 450% of baseline within 40 min postinjection (Fig. 3). Thereafter, DA concentrations steadily decreased, approaching baseline by the end of experiment (180 min). Pretreating animals with APZ 5 mg/kg had no effect on AMPH-induced DA increase. APZ 10 mg/kg somewhat attenuated DA increase, but after 60 min there was no difference compared to the AMPH group. An overall ANOVA of DA values showed that neither treatment, $F(2, 15) = 1.34$, nor treatment × time interaction, $F(18, 135) = 0.829$, effects were significant. Only time effect was significant, $F(9, 135) = 27.9$, $p < 0.001$ (Fig. 3).

DOPAC levels decreased after AMPH administration, reaching 60% of baseline within 40 min. There was significant treatment effect, $F(2, 15) = 10.3$, $p = 0.002$, but no treatment × time interaction effect. Posthoc analysis revealed sig-

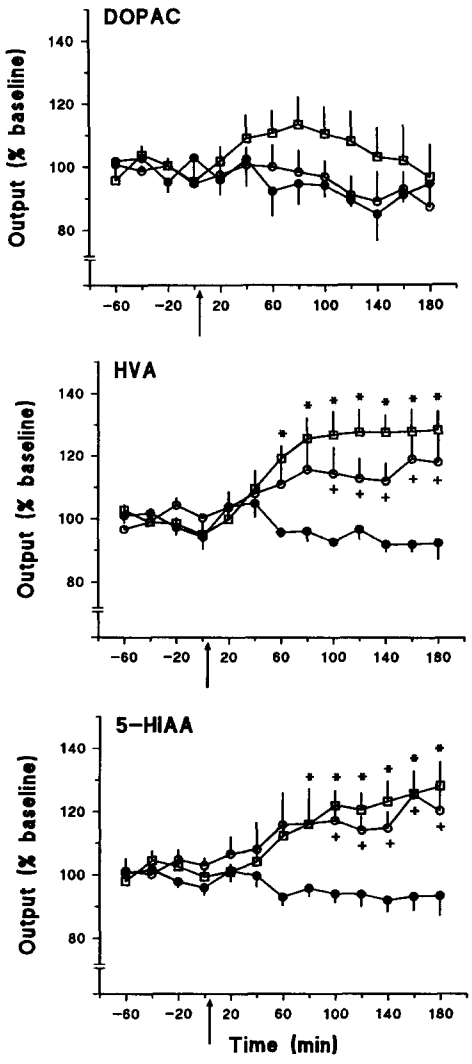

FIG. 2. Effect of amperozide (APZ) (5 mg/kg, SC, ○, n = 5; 10 mg/kg, SC, □, n = 6) or saline (1.0 mg/kg, SC, ●, n = 6) on dialysate concentrations of dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) from the nucleus accumbens. Each point represents the mean percent change of baseline. The overall mean ± SEM basal values of DOPAC, HVA, and 5-HIAA were 323.2 ± 22.8, 183.6 ± 12.5, and 242.7 ± 13.4 fmol/min (n = 17), respectively. The arrow indicates injection of drug or vehicle. †$p < 0.05$ APZ 5 compared to saline; *$p < 0.05$ APZ 10 compared to saline.

nificant differences ($p < 0.05$) between AMPH and APZ 5 mg/kg + AMPH at 20 and 40 min postinjection. Additional posthoc comparisons showed significant differences between AMPH and APZ 10 mg/kg + AMPH for all time points except 40 and 60 min postinjection (Fig. 4).

HVA concentrations slightly decreased to 82% 80 min after AMPH administration, followed by a return to baseline 60 min later. Both treatment effect, $F(2, 15) = 8.73, p = 0.003$, and treatment × time interaction effect, $F(18, 135) = 2.46$, $p = 0.002$, were significant. Pretreatment with 5 mg/kg APZ did not influence the AMPH-induced decrease in HVA, whereas 10 mg/kg APZ reversed the effect of AMPH on HVA at all time points except 40, 60, and 100 min postinjection (Fig. 4, middle panel).

Effects of APZ on 5-HIAA concentrations were significant for treatment, $F(2, 15) = 4.40$, $p = 0.03$, but not for treatment × time interaction effect. Posthoc analysis revealed significant increases ($p < 0.05$) in animals pretreated with APZ 10 mg/kg for 3 of 10 data points (Fig. 4).

Effect of APZ on COC-Induced Changes of Dialysate Concentrations of DA, Its Metabolites, and 5-HIAA From the NAC

There was no difference in mean values of basal DA and its metabolites among the treatment groups: DA, $F(2, 15) = 0.31$; DOPAC, $F(2, 15) = 1.24$; HVA, $F(2, 15) = 0.35$; 5-HIAA, $F(2, 15) = 1.06$.

Administration of COC increased DA concentrations to approximately 270% of baseline within 40 min postinjection. DA levels gradually decreased thereafter. An overall ANOVA on DA values showed that neither treatment, $F(2, 15) = 0.63$, $p = 0.55$, nor treatment × time, $F(18, 135) = 1.59$, $p = 0.07$, effects were significant. Only time effect was significant, $F(9, 135) = 44.13, p < 0.001$ (Fig. 5).

DOPAC levels decreased after COC administration, reaching 70% of baseline after 80 min postinjection. DOPAC levels remained around this range for 60 min more, then approached baseline at the last sample time. Pretreatment with APZ attenuated this decrease. All effects were significant: treatment, $F(2, 15) = 6.03$, $p = 0.01$, time, $F(9, 135) = 16.01$, $p < 0.001$, and treatment × time, $F(18, 135) = 2.29, p < 0.001$. Posthoc comparisons showed significant differences ($p < 0.05$) in five data points with pretreatment of APZ 5 mg/kg and four data points with pretreatment of APZ 10 mg/kg (Fig. 6).

HVA output also declined after COC injection, the lowest point being 90% of baseline at the 80-min mark. All effects were significant: treatment, $F(2, 15) = 5.68$, $p = 0.01$, time,

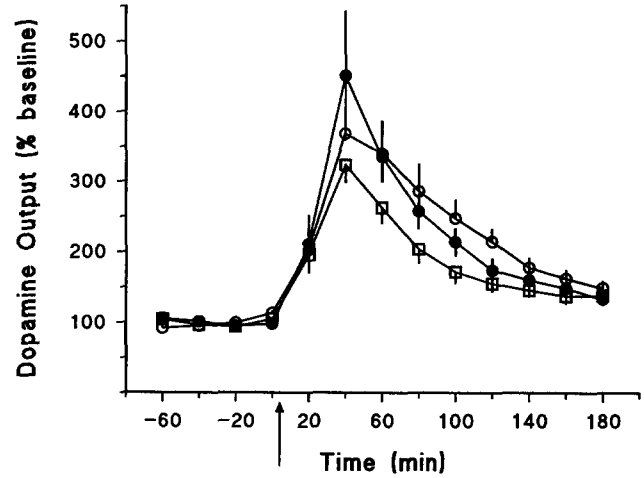

FIG. 3. Effect of amperozide (APZ) (5 mg/kg, SC, ○, n = 5; 10 mg/kg, SC, □, n = 5) on amphetamine (AMPH) (1.0 mg/kg, SC, ●, n = 8)-induced changes in dialysate concentrations of dopamine (DA) from the nucleus accumbens. Each point represents the mean percent change of baseline. The overall mean ± SEM basal value of DA was 3.19 ± 0.55 fmol/min (n = 18). The arrow indicates injection of AMPH.

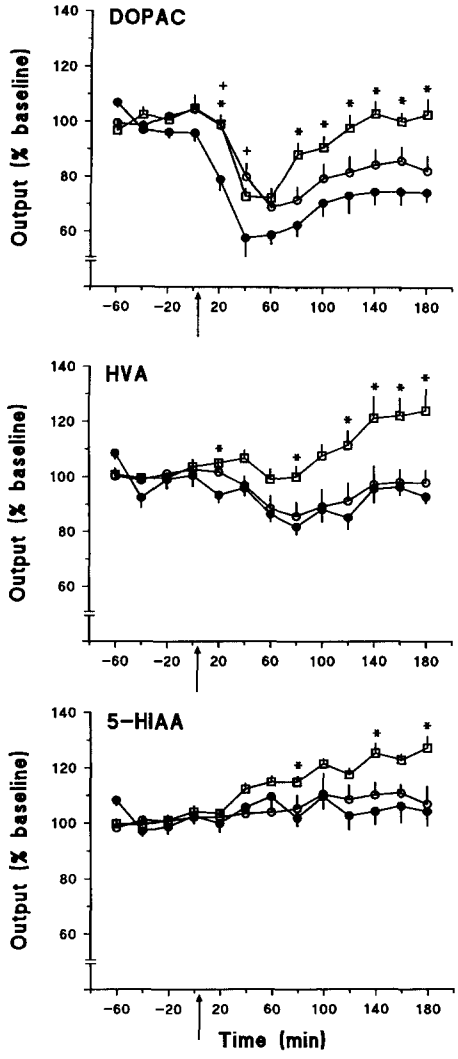

FIG. 4. Effect of amperozide (APZ) (5 mg/kg, SC, ○, n = 5; 10 mg/kg, SC, □, n = 5) on amphetamine (AMPH) (1 mg/kg, SC, ●, n = 8)-induced changes in dialysate concentrations of dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) from the nucleus accumbens. Each point represents the mean percent change of baseline. The overall mean ± SEM basal values of DOPAC, HVA, and 5-HIAA were 392.5 ± 37.6, 220.0 ± 20.7, and 290.6 ± 21.1 fmol/min (n = 18), respectively. The arrow indicates injection of amphetamine. †p < 0.05 APZ 5 compared to AMPH; *p < 0.05 APZ 10 compared to AMPH.

$F(9, 135) = 6.83$, $p = 0.000$, and treatment × time, $F(18, 135) = 2.02$, $p = 0.01$. Posthoc comparisons revealed significant ($p < 0.05$) effects 60 min after injection. Pretreatment with APZ dose dependently reversed the COC-induced decrease in HVA (Fig. 6).

Sixty minutes after COC injection, 5-HIAA output decreased to 90% and remained at this range during the rest of experiment. All effects were significant: treatment, $F(2, 15) = 5.54$, $p = 0.02$, time, $F(9, 135) = 3.76$, $p = 0.00$, and treatment × time, $F(18, 135) = 2.22$, $p = 0.01$. Posthoc analysis showed significant ($p < 0.05$) effects at 80, 120, 140, and 180 min (Fig. 6).

DISCUSSION

This study assessed effects of an atypical antipsychotic drug, APZ, on both spontaneous activity and psychostimulant-induced hypermotility in relation to changes in interstitial concentrations of DA in the NAC as measured by in vivo microdialysis. Doses of APZ used in this study were higher than those previously shown to reduce hyperlocomotion (14,23), but prior experiments (50) have indicated that higher doses of APZ are required to induce biochemical effects compared to behavioral actions. Our results demonstrate that APZ inhibited motor activity in both control and AMPH- or COC-treated animals. APZ dose dependently increased DA, HVA, and 5-HIAA concentrations in the NAC. APZ pretreatment did not influence AMPH- or COC-induced increases in interstitial concentrations of DA in the NAC.

Effects of APZ on Locomotor Activity

APZ dose dependently reduced the following motor activity measurements: horizontal activity, forward locomotion, and rearing. Corner time measurements most likely reflect the amount of time animals spent resting. The finding that APZ increased corner time indicates reduced motor activity of rats. The present data are in agreement with previous studies with mice (14,23) and rats (68).

The finding that APZ reduced spontaneous locomotion is similar to behavioral effects of other neuroleptics. Both typical and atypical neuroleptics decrease motor activity (2,23,59,64), presumably through DA receptor blockade. The observed effects of APZ might not be readily attributed to DA receptor blockade because in vitro binding studies have demonstrated weak D_2 receptor affinity. On the other hand, it is difficult to explain the observed hypomotility by other known biochemical properties of APZ. For example, neither 5-HT_2 receptor antagonists (47) nor 5-HT reuptake inhibitors (6,20) influence spontaneous locomotion. The selective α_1-receptor blocker, prazosin, also failed to affect spontaneous motor behavior (13,62).

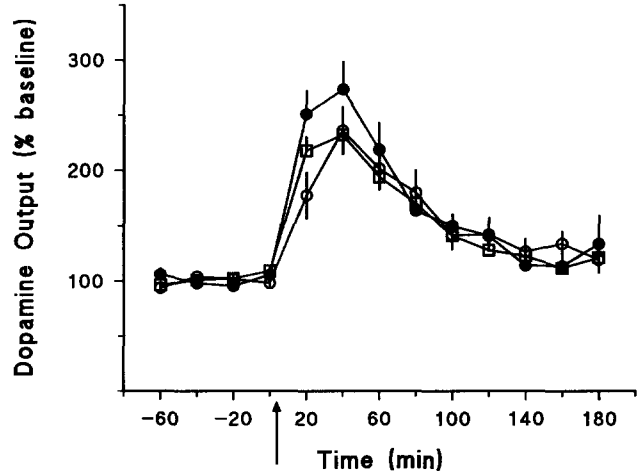

FIG. 5. Effect of amperozide (APZ) (5 mg/kg, SC, ○, n = 6; 10 mg/kg, SC, □, n = 6) on cocaine (COC) (10 mg/kg, IP, ●, n = 6)-induced changes in dialysate concentrations of dopamine (DA) from the nucleus accumbens. Each point represents the mean percent change of baseline. The overall mean ± SEM basal value of DA was 1.61 ± 0.21 fmol/min (n = 18). The arrow indicates injection of COC.

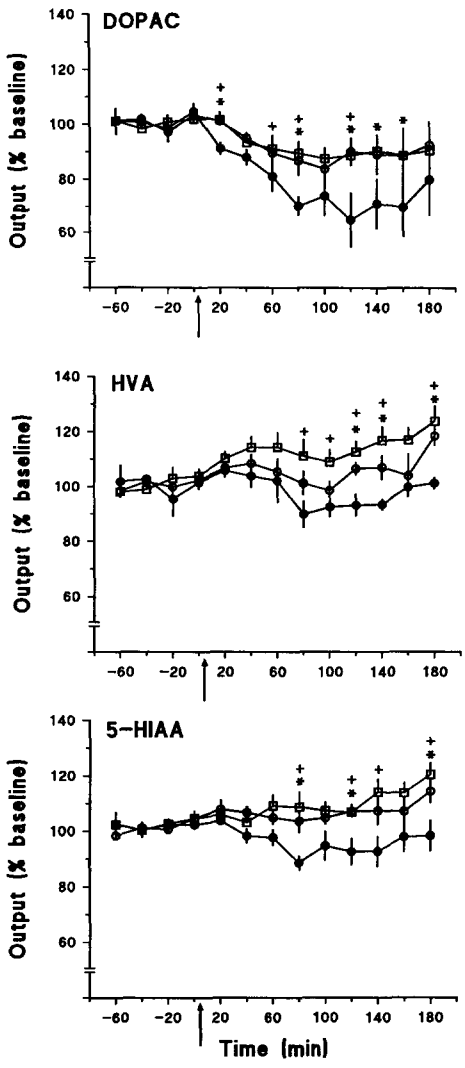

FIG. 6. Effect of amperozide (APZ) (5 mg/kg, SC, ○, n = 6; 10 mg/kg, SC, □, n = 6) on cocaine (COC) (10 mg/kg, IP, ●, n = 6)-induced changes in dialysate concentrations of dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) from the nucleus accumbens. Each point represents the mean percent change of baseline. The overall mean ± SEM basal values of DOPAC, HVA, and 5-HIAA were 324.2 ± 23.4, 177.4 ± 10.7, and 251.3 ± 11.8 fmol/min (n = 18), respectively. The arrow indicates injection of COC. †$p < 0.05$ APZ 5 compared to COC; *$p < 0.05$ APZ 10 compared to COC.

Effect of APZ on AMPH- and COC-Induced Hyperlocomotion

AMPH and COC stimulated motor activity in all indices except rearing in AMPH-treated rats. APZ pretreatment antagonized both AMPH- and COC-induced hypermotility. The present results on the effects of APZ pretreatment on AMPH-induced hyperlocomotion are in accordance with previous reports (14,23,68). The effects of APZ on hypermotility induced by COC further confirmed behavioral antagonism by APZ pretreatment. It is noteworthy that similar reductions in horizontal activity, forward locomotion, and rearing measurements were seen in both control and AMPH- or COC-treated animals (see percent changes, Tables 1 and 2). Thus, in this study the effects of APZ on psychostimulants could not be differentiated from the actions of APZ itself on locomotion. However, previous studies using lower doses of APZ demonstrate inhibition of AMPH-induced hyperlocomotion without altering spontaneous behavior (14). It is interesting that in the present study a clear antagonism of psychostimulant-induced behavior by APZ pretreatment was observed in corner time measurements.

It is well established that DA receptor blocking agents antagonize hyperlocomotion induced by psychostimulants (15,23,38,48,60,64). The property of APZ to block hypermotility induced by both AMPH and COC suggests antagonism of DA receptors as a possible mechanism of action. However, this is not fully supported by in vitro studies showing only weak affinity of APZ for DA receptors. Therefore, the effects of APZ on presynaptic DA mechanisms or other neurotransmitter systems must be considered.

There is evidence that APZ may act as a DA uptake inhibitor (17,18). DA uptake inhibitors have been shown to antagonize psychostimulant-induced motor behaviors (21,51,57), but these agents increase locomotor activity when administered alone. Such stimulatory effects can be detected with APZ (68) but only at higher doses than the ones used in the present study.

APZ has been shown to possess affinity for both 5-HT_2 receptors and 5-HT uptake sites (17,25,40,63). However, 5-HT_2 antagonism could not account for the observed effects because ritanserin, a moderately selective 5-HT_2 antagonist, has no effect on AMPH-stimulated hyperlocomotion (47). Likewise, the 5-HT uptake inhibiting property of APZ could not account for the present results as fluoxetine, a selective 5-HT reuptake inhibitor, has failed to antagonize locomotor stimulatory effects of AMPH (6,66).

APZ has also been shown to possess moderate affinity for α_1-adrenergic receptors. There is some evidence that α_1-adrenoceptors may be involved in locomotor activity. Previous studies have demonstrated that pretreatment with prazosin reduced motor behavior induced by DA agonists (13,62,65). Therefore, it seems likely that α_1-blocking properties are involved in the observed actions of APZ on psychostimulant-mediated hypermotility.

Effects of APZ on DA, Its Metabolites, and 5-HIAA

APZ dose dependently increased DA and HVA concentrations and tended to increase DOPAC concentrations. One plausible explanation for these effects could be DA receptor blockade. Previous studies have shown that DA receptor antagonists increase DA concentrations in the striatum and NAC (30,31). It should be also noted that all neuroleptics, both typical and atypical, consistently increase dialysate concentrations of DA and its metabolites (30,31,42,61,69,70,72). However, the increases seen with APZ are considerably less than those reported with other DA receptor antagonists or other neuroleptics. This, together with in vitro results, suggests that APZ is only a weak DA receptor blocker in vivo.

The effects of APZ on dialysate concentrations of DA and its metabolites most closely resemble those of nomifensine, a DA uptake blocker (5). Nomifensine also increased basal DA and HVA efflux while not affecting DOPAC. However, APZ differs from other DA uptake inhibitors. For example, GBR12909 also produces a modest increase in DA release in rat striatum but fails to affect DOPAC and HVA levels (69). In addition, COC has been shown to actually decrease

DOPAC and HVA [(3,4,34,37), this study]. Bupropion, a weak but selective DA uptake inhibitor, increases DA, decreases HVA, and tends to decrease DOPAC in the NAC (45). Considering the variable effects of DA uptake blockers on DA metabolites, we cannot exclude the possibility that DA uptake inhibiting properties of APZ contribute to the observed effects on DA and its metabolites.

The effects of APZ on serotonergic systems should also be considered as it has been suggested that the potent 5-HT_2 receptor properties of APZ may play a role in its effects on DA-mediated behavioral and biochemical responses. In a recent study, ritanserin has been shown to increase dialysate concentrations of DA from the NAC (11). However, ritanserin, in contrast to APZ, fails to significantly alter DA metabolites. On the other hand, it is difficult to attribute the effects of APZ on DA transmission to the 5-HT uptake inhibitory property of APZ. Fluoxetine, for example, has no effect on DA concentrations as measured by in vivo microdialysis (44). Hence, the 5-HT_2 receptor antagonism but not 5-HT uptake inhibition properties of APZ may have influenced DA release. In contrast to the recent report by Ichikawa and Meltzer (29), who found no effects of APZ on 5-HIAA dialysate concentrations from the striatum and NAC, we observed a significant increase in 5-HIAA levels with both doses of APZ. The reason for this disparity is unclear, but it should be noted that there appears to be a complex relationship between interstitial concentrations of 5-HIAA and serotonergic transmission (33). The observed increase in 5-HIAA in the present study may be related to actions of APZ on either 5-HT_2 receptors or 5-HT uptake sites or both. However, neither ritanserin nor 5-HT uptake inhibitors, such as indalpine or fluoxetine, influence significantly 5-HIAA dialysate concentrations (11, 33,73).

Effects of APZ on AMPH- and COC-Induced DA Release, DA Metabolites, and 5-HIAA

Administration of AMPH and COC resulted in 450 and 270% increase in DA concentrations, respectively, in the NAC. These data are in agreement with previous studies in which similar changes in dialysate concentrations of DA were observed (3–5,28,34,37,41,46,52,55).

In contrast to the results reported by Ichikawa and Meltzer (29), we were not able to demonstrate that APZ pretreatment attenuated AMPH-induced DA release in the NAC. The present data further revealed that APZ pretreatment also failed to affect COC-induced increase in DA concentrations from the NAC. Ichikawa and Meltzer observed that APZ dose dependently antagonized AMPH-induced DA release in both the striatum and NAC. It is noteworthy that in their study the AMPH-induced DA release was considerably greater than generally reported (5,7,12,36,37,46,52,54–56,61,71). This was explained by differences in $C\alpha^{2+}$ concentration in the perfusion solutions used that might have influenced basal and stimulated DA release [see p. 2288 of (29)]. However, other studies using low $C\alpha^{2+}$ concentrations have demonstrated that the magnitude of AMPH-induced DA release was still lower than that observed by Ichikawa and Meltzer (5,36,37,46,54).

An alternative explanation may be the postimplantation time interval (24 h) used by Ichikawa and Meltzer. There is evidence that the time interval between probe implantation and dialysis experiment is a critical factor in stimulated neurotransmitter release and that longer postimplantation intervals, as used in the present study (40–48 h), more closely reflect the physiological state (10,55,74). This may explain the discrepancy in the ability of APZ to antagonize the enhanced DA release following AMPH seen in the two studies.

Neuroleptics potentiate the increase in DA concentration induced by either AMPH, AMPH analogs, or DA uptake inhibitors (61,67,69). The lack of such synergistic effects in our results is consistent with previous reports demonstrating weak DA receptor affinity of APZ. From other known biochemical properties of APZ such as DA and 5-HT uptake inhibition, and 5-HT_2 receptor antagonism, we would expect attenuation of DA release elicited by psychostimulants. For example, nomifensine and GBR12909 attenuate AMPH- and COC-induced DA increase, respectively (5,58). Fluoxetine and ketanserin, a 5-$HT_{2/1c}$ antagonist, also inhibit DA release induced by an AMPH analog (43,44). Our findings are not compatible with the above reports. Thus, the actions of APZ in vivo are not in accordance with its reported in vitro biochemical characteristics of potent 5-HT_2 receptor affinity and moderate DA and 5-HT affinity for uptake sites. This is further supported by the effects of APZ alone on DA transmission (see the discussion above).

APZ pretreatment dose dependently attenuated the decreases in DA metabolites induced by AMPH and COC. The most likely explanation for these effects is the finding that APZ alone enhances DA turnover. In general, the increase in dialysate concentrations of DA metabolites induced by neuroleptics most likely reflects enhanced DA synthesis (69,70). In this effect, both pre- and postsynaptic DA receptors appear to participate (69,70). It is interesting, however, that APZ fails to antagonize apomorphine-induced inhibition of DA synthesis rate (68) and VTA-DA neuronal activity (22). Despite the aforementioned results, the present data do not exclude a role of DA receptors in mediating the biochemical actions of APZ.

Dissociation Between Behavioral and Biochemical Data

In summary, the effects of APZ on spontaneous locomotion and on hyperlocomotion elicited by AMPH and COC resemble those of DA receptor antagonists. There is additional possibility of α_1-receptor involvement in the blockade of psychostimulant-induced hypermotility. On the other hand, the DA receptor antagonism and DA uptake inhibition properties of APZ may play a role in the observed effects of DA and its metabolites in the microdialysis experiments. As discussed, the effects of APZ on basal and psychostimulant-induced DA release in NAC could not be solely attributed to known biochemical properties of APZ demonstrated in vitro. Rather, they reveal a more complex profile in which the different mechanisms of action of APZ appear to merge.

The antagonism of AMPH- and COC-induced hyperlocomotion by APZ was not accompanied by changes in DA release induced by the psychostimulants. The behavioral effects of APZ may be attributed to interactions among the different neurotransmitter systems within an organism. Such interactions are not necessarily reflected in changes in dialysate DA concentrations from the NAC. Thus, the blockade of AMPH- and COC-induced hyperlocomotion could be due to effects of APZ on postsynaptic sites within or beyond the NAC that do not affect DA release. There are accumulating reports of such dissociation between DA release in terminal regions and behavior induced by psychostimulants (2,34,36,37,45). The present study further supports these observations.

Given the clinical relevance of the effects of atypical neuroleptics on forebrain dopaminergic systems, the elucidation of the mechanisms and sites of action of APZ is of particular

importance. Recent studies have indicated that atypical neuroleptics exert distinctive effects on DA transmission in the prefrontal cortex (42,53). In addition, there is some evidence that the prefrontal cortex is involved in mediation of stimulatory properties of psychostimulants (8,19,32). Therefore, it may be worthwhile to examine the effect of systemic and topical administration of APZ on basal and AMPH- and COC-induced DA release in the prefrontal cortex.

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