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RAPID COMMUNICATION

Amperozide, a 5-HT_2 Antagonist, Attenuates Craving for Cocaine by Rats

BRIAN A. McMILLEN,*[1] ELIZABETH A. JONES,* LARA J. HILL,* HELEN L. WILLIAMS,* ANDERS BJÖRK† AND R. D. MYERS*

**Department of Pharmacology and Center for Alcohol and Drug Abuse Studies, School of Medicine, East Carolina University, Greenville, NC 27858*
†Kabi Pharmacia AB, Business Unit CNS, Malmö, Sweden

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McMILLEN, B. A., E. A. JONES, L. J. HILL, H. L. WILLIAMS, A. BJÖRK AND R. D. MYERS. *Amperozide, a 5-HT_2 antagonist, attenuates craving for cocaine by rats.* PHARMACOL BIOCHEM BEHAV **46**(1) 125–129, 1993.—Amperozide, a novel 5-HT_2 receptor antagonist with little affinity for the dopamine receptor, suppresses the intake of alcohol in rats without affecting food intake or inducing other side effects. Because of these actions, amperozide was examined for its efficacy on the oral preference by the rat for a solution of cocaine. In this study, rats were selected for their voluntary consumption of at least 10 mg/kg of cocaine per day in a two-choice paradigm. A solution of 0.02% to 0.06% cocaine plus 0.03% saccharin in water was offered to each animal simultaneously with a solution of only 0.03% saccharin in water. The consumption of food and both fluids, as well as body weight, was recorded daily for three successive periods: 4 days of pretreatment baseline; 3 days during injections of either amperozide or the saline vehicle solution; and 4 days postinjections. Amperozide was administered SC twice daily in a dose of 0.5, 1.0, or 2.5 mg/kg. The volitional intake of cocaine was significantly reduced not only during the 3-day period of injections of amperozide but also during the 4-day posttreatment period. Amperozide exerted little or no effect on the intake of food or on body weight. Radioligand binding experiments confirmed that amperozide has at least a twentyfold greater affinity for 5-HT_2 receptors in the frontal cortex of the rat, as compared to striatal DA_1 and DA_2 receptors, with the proportion value similar to that of the 5-HT_2 receptor antagonist, ritanserin. It is concluded, therefore, that amperozide, which produces little or no adverse side effects, appears to be potentially useful for the treatment of the addiction to cocaine.

Amperozide Cocaine Serotonin Drinking Addiction 5-HT receptors Self-administration Brain

COCAINE is a member of the nonamphetamine class of central nervous system stimulants (16) that release dopamine (DA) by mobilizing a large reserpine-sensitive storage pool (17,34). Since cocaine has similar potencies for the inhibition of reuptake of DA, noradrenaline, and serotonin (5-HT) (33,37), an alteration in the activity of these neurotransmitters apparently mediates the overall behavioral effects of cocaine. Cocaine increases extracellular concentrations of DA in the nucleus accumbens in vivo (3,4,28), and this excess release of DA within mesolimbic structures of the brain is thought to comprise, in part, the rewarding component of cocaine (14). Further, the potency for inhibition of DA reuptake correlates with the potency for either CNS stimulation (17) or the intravenous self-administration of cocaine (30).

Further evidence for the involvement of the mesolimbic dopaminergic system in the reward mechanisms of stimulant drugs is provided by the fact that an impairment of dopaminergic activity reduces the reward component of cocaine. For example, the lesioning of dopaminergic neurons in the mesolimbic system (31,32) or blockade of the DA_1 or DA_2 receptor reduces the self-administration of cocaine (7,12). However, the reduction of intravenous self-administration of cocaine due to the impairment of dopaminergic function may not equate with the reduction of craving for cocaine. In addition, antagonists of DA receptors can produce untoward extrapyramidal side effects. Thus, a drug devoid of both neuroleptic activity and addictive liability, which possesses its mechanism of action for reducing cocaine craving within the limbic system, would represent a major advance in the therapy of cocaine abuse.

[1] To whom requests for reprints should be addressed.

The search for a drug that not only blocks the craving for cocaine but reduces the recidivism in the cocaine addict has taken three different directions. These include treatment with narcotic drugs (18) as well as drugs that modify either dopaminergic activity (6,7,11,12) or serotonergic activity in the brain (19). The serotonergic drug, amperozide, is known to modify slightly the basal release of DA in the mesolimbic system but to exert little effect on the concentration of DA or its metabolites assayed in brain tissue (29). In terms of its central actions, amperozide attenuates locomotor behavior induced by amphetamine (10); in addition, amperozide evokes the release of DA within the mesolimbic system but serves to diminish the release of DA stimulated by amphetamine (13). Amperozide has a high affinity for the 5-HT_2 receptor and a much lower affinity for DA receptors and DA reuptake sites in brain tissues (9,21,36). In addition, amperozide has a high affinity for the serotonergic reuptake site (Svartengren, personal communication) and has an IC_{50} against 5-HT uptake into synaptosomes of 0.32 μM (9).

Recently, it was shown that amperozide inhibits the voluntary consumption of ethyl alcohol by rats induced to drink large amounts of alcohol by prior treatment with cyanamide (23). Of interest is the finding that the ameliorative effect of amperozide on alcohol consumption is apparently irreversible (26). Further, amperozide exerts the same action in reducing the volitional intake of high concentrations of alcohol in the genetically bred line of alcohol-preferring (P) rats (27). Although another 5-HT_2 antagonist, ritanserin, reportedly reduces drinking of a mild alcohol solution (19), this result has not been replicated (24). Taken together, these data suggested to us that amperozide possesses a potential to reduce craving for cocaine without interfering directly with DA receptors, and may provide a preferred method for reducing the craving for cocaine. The purpose of this investigation, therefore, was to determine whether amperozide would alter the self-administration of a preferred cocaine solution in a free-choice situation.

METHOD

Animals

Two groups of 13 Sprague–Dawley rats, weighing 225–250 g at the time of purchase (Charles River Laboratories, Raleigh, NC), were housed individually in suspended stainless steel cages in an animal room with lights on at 0600 and off at 2000 h. Three calibrated drinking tubes were placed on the front of each cage and rotated on each day, according to a semirandomized sequence, to prevent the occurrence of a position habit (23).

Cocaine Drinking

The procedure for testing the oral preference for cocaine was conducted twice. In an initial taste comparison between 0.05% aspartame and 0.05% effervescent saccharin, it was found that the rats exhibited a strong preference for the saccharin solution. Following this determination, a period of drinking of 0.01% cocaine (NIDA, Rockville, MD) in the saccharin solution, with no other solution available, was initiated. The concentration of cocaine was then increased in 0.01% steps daily until the mg/kg amount consumed per day declined. Under this condition, many of the rats drank over 100 mg/kg per day of 0.08% cocaine dissolved in the 0.05% saccharin solution.

The concentration of saccharin subsequently was reduced for all animals over 2 days to 0.03%, which was the final concentration used over the remainder of the study. After a 2-day test was conducted with water in one tube and 0.02% cocaine in saccharin in the other, the cocaine/saccharin solution was tested against saccharin only. The third drinking tube, which was always empty, served to deter a position habit (23). Each day the concentration of cocaine was increased or decreased by 0.01% until the maximal mg/kg per day was determined individually for each rat over a period of 7 days. Of the 26 rats tested originally, 13 drank 10 mg/kg per day or more and were used for subsequent studies.

Experimental Design

A 4-day predrug treatment period was used to establish daily baseline values for the amounts of food consumed, total liquid ingested, the mg/kg per day cocaine taken, and the proportion of ml of the cocaine/saccharin solution to the total intake of both the cocaine/saccharin and saccharin only solutions. Amperozide-HCl (Kabi Pharmacia Business Unit AB, Malmo, Sweden) was prepared on each day in doses based on our earlier studies (26,27) of 0.5, 1.0, or 2.5 mg/kg in 0.9% saline control vehicle. One of the doses of amperozide or the saline vehicle was injected SC, according to a randomized sequence, at 1600 and 2200 h for 3 consecutive days, after which the preference for cocaine was tested for a 4-day posttreatment period. Although nine rats received all four treatments, four rats did not return to their baseline intakes of cocaine following one of the drug treatments and thus were excluded from further study. A repeated measures analysis of

TABLE 1

EFFECT OF AMPEROZIDE ON FOOD, LIQUID, AND COCAINE CONSUMPTION BY SPRAQUE-DAWLEY RATS

Treatment (*n*)	Pre*	During	Post
	Food (g/day)		
Saline (10)	31.1 ± 1.6	32.9 ± 1.0	32.6 ± 1.0
0.5 (10)	34.4 ± 1.1	30.4 ± 1.1†	30.6 ± 1.4†
1.0 (9)	35.4 ± 1.3	30.7 ± 0.5†	32.7 ± 1.2†
2.5 (9)	32.9 ± 1.2	27.4 ± 1.1†	30.9 ± 1.5‡
	Total Liquids (ml/day)		
Saline (10)	76.4 ± 5.3	68.7 ± 3.7†	72.1 ± 5.3
0.5 (10)	67.8 ± 6.3	51.1 ± 5.5†	66.4 ± 8.0
1.0 (9)	75.2 ± 6.6	51.7 ± 2.9†	72.3 ± 4.5
2.5 (9)	70.8 ± 6.9	53.0 ± 4.3†	65.8 ± 5.9
	Proportion (ml cocaine/ml total)		
Saline (10)	0.53 ± 0.08	0.50 ± 0.08	0.58 ± 0.09
0.5 (10)	0.66 ± 0.05	0.50 ± 0.08†	0.52 ± 0.06
1.0 (9)	0.58 ± 0.09	0.44 ± 0.09‡	0.53 ± 0.09
2.5 (9)	0.62 ± 0.08	0.54 ± 0.07	0.54 ± 0.08
	Cocaine (mg/kg/day)		
Saline (10)	28.4 ± 4.9	24.5 ± 4.8	28.3 ± 4.8
0.5 (10)	33.7 ± 5.3	17.9 ± 3.6†	25.2 ± 4.5†
1.0 (9)	30.3 ± 5.2	17.5 ± 4.7‡	26.5 ± 4.6
2.5 (9)	31.3 ± 4.9	21.5 ± 4.7‡	25.7 ± 4.7

*Each rat had a 4-day pretreatment baseline period, 3-day treatment with saline or different doses of amperozide twice daily, and a 4-day posttreatment period.

†‡Different from predrug period (Tukey's HSD): †$p < 0.01$, ‡$p < 0.05$.

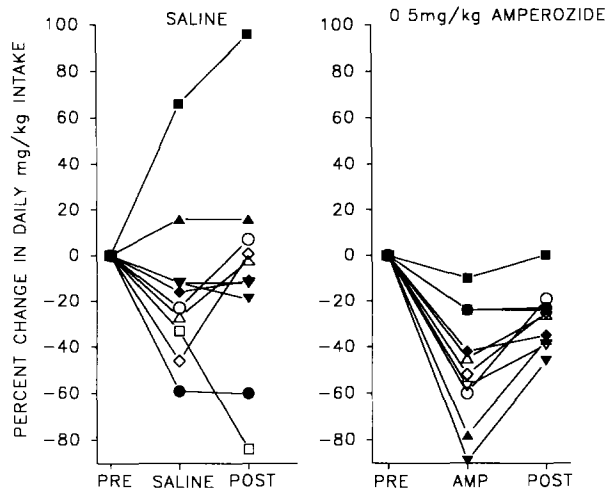

FIG. 1. Individual data for percent change in cocaine consumption from the 4-day pretreatment to the 3-day treatment period with either saline or 0.5 mg/kg amperozide, administered SC twice daily, and the 4-day posttreatment periods. The 4-day pretreatment period was taken as control for each rat.

variance followed by Tukey's HSD test (GB-Stat, Dynamic Microsystems, Silver Spring, MD) was used to compare each measure obtained during the baseline with the values during the treatment of each dose of amperozide, as well as during the posttreatment period of testing (38).

Radioligand Displacement

The affinities of amperozide and ritanserin for DA_1, DA_2, and 5-HT_2 receptors on washed membrane preparations were determined by previously described methods (18,35). Striatal membrane DA_1 receptors were labeled with 0.5 nM [^{3}H]SCH-23390 (DuPont-NEN, Boston, MA) and DA_2 receptors with 0.1 nM [^{3}H]spiperone (Amersham, Chicago, IL). Frontal cortex membrane 5-HT_2 receptors were labeled with 0.1 nM [^{3}H]spiperone with 0.1 μM (*l*)-sulpiride added to mask the DA_2 receptor. The values for IC_{50} were used to calculate values for K_i (5).

RESULTS

Twice daily injections of amperozide in the rats reduced the preference for the individual solutions of cocaine both during and after treatment with the drug. As shown in Table 1, the consumption of cocaine was attenuated significantly by amperozide given in daily doses of 0.5 mg/kg, $F(2, 9) = 18.94$, $p < 0.01$, 1.0 mg/kg, $F(2, 8) = 7.26$, $p < 0.01$, and 2.5 mg/kg, (F2, 8) = 3.30, $p < 0.05$. Overall, the mean amount of cocaine consumed per day declined by 47% after the 0.5-mg/kg dose and by 32% following the 2.5-mg/kg dose of amperozide. As shown in Fig. 1, the greatest effect of amperozide occurred following the 0.5-mg/kg dose of the drug, which persisted during the 4-day postdrug period. Thus, in this experiment, amperozide did not exhibit a clear-cut dose-response relationship (Table 1). In contrast to amperozide, the injections of saline vehicle did not uniformly reduce the drinking of the cocaine solutions (Fig. 1).

The proportion of cocaine-containing fluid consumed to total fluid consumed also declined (Table 1), which reflected

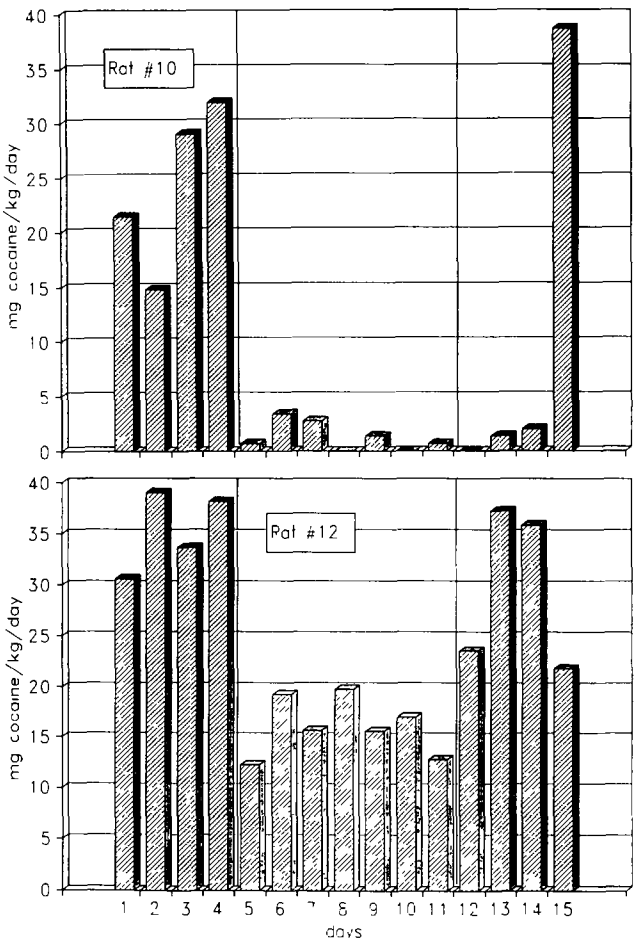

FIG. 2. Daily cocaine intake by two individual rats. A 4-day pretreatment period preceded 7 days of injections of 2.5 mg/kg amperozide twice daily, which was followed by a 4-day posttreatment period. Injections of amperozide were made at 1600 and 2200 h beginning after recording cocaine intake on the fourth pretreatment day.

the shift in drinking to the solution containing only saccharin. Amperozide also caused a reduction in the total intake of fluid ingested, which was largely due to a decrease in drinking of the cocaine solution. Although the same doses of amperozide induced a dose-related decrease in alcohol drinking in the rat (25), they exerted little or no effect on the ingestion of food or on body weight (8). In the present study, however, the intake of food was attenuated by 11.6% after 0.5-mg/kg amperozide and 16.7% after 2.5-mg/kg amperozide. Thus, amper-

TABLE 2

AFFINITIES (K_i) OF AMPEROZIDE AND RITANSERIN FOR STRIATAL DA_1 AND DA_2 AND FRONTAL CORTEX 5-HT_2 RECEPTORS

	DA_1	DA_2	5-HT_2
Amperozide	496 ± 43 (3)	782 ± 105 (6)	24 ± 2 (3)
Ritanserin	91 ± 8 (4)	25 ± 9 (4)	5 ± 2 (3)

Values are nM ± SEM (*n* independent determinations).

ozide exhibited a weak, but significant, dose-response relationship on food consumption. Although the consumption of food and cocaine remained suppressed during the 4-day posttreatment period (significant for intake of food, Table 1), the body weights of the rats were unaffected by any dose of amperozide and continued to increase slightly during the postdrug period.

Two rats from this experiment, which typically consumed more than 20–35 mg/kg per day of cocaine, were given amperozide for a longer injection period of 7 days. Figure 2 illustrates the marked decline in the amount of cocaine consumed by the animals during the 7-day period of injections of 2.5-mg/kg amperozide given twice daily. Rat #12 resumed its normal consumption of cocaine on the second day after the end of treatment, whereas the intake of cocaine by rat #10 rebounded on the fourth posttreatment day. However, this rat never consumed significant quantities of cocaine thereafter. In an attempt to increase the intake of cocaine by this rat, the cocaine/saccharin solution was presented alone for an additional 3 days; nevertheless, its intake remained at a minimal level observed during the amperozide treatment when the two-choice paradigm was resumed.

To compare the relative affinities of amperozide at 5-HT_2 and dopamine receptors, a radioligand receptor displacement study was conducted. Ritanserin, which is considered to be a typical 5-HT_2 receptor antagonist (15), was used for this comparison. Table 2 compares the affinities of amperozide and ritanserin for the DA_1, DA_2, and 5-HT_2 receptor sites. The value of 24 nM for the affinity of amperozide at the frontal cortex 5-HT_2 binding site compares closely with the value of 23 nM reported previously (36). Thus, the relative preference of amperozide for the 5-HT_2 binding site over dopaminergic receptors is similar in proportion to ritanserin, whereas neither drug has an affinity for DA receptors that approaches their affinity for the 5-HT_2 binding site.

DISCUSSION

The present results show that amperozide has a potent inhibitory effect on the oral consumption of cocaine. In contrast to the action of amperozide on alcohol drinking (25), a dose-response relationship did not emerge, which suggests that even lower doses may be required to establish such a relationship. Amperozide exerted a minimal effect on the consumption of food as well as on body weight, which indicates that the rats tolerate these doses well. As shown by the data in Fig. 2, the effect of amperozide is maintained during a longer period of treatment. In accord with this result is the finding that the constant infusion of 5.0 mg/kg per day amperozide SC causes a sustained decline in the drinking of alcohol by rats induced to drink alcohol by cyanamide (26).

Another 5-HT_2 antagonist, ritanserin, reportedly reduced the drinking of a cocaine solution, but in an average daily quantity that approximated one-third of the amount selected freely by the rats in the present study (19). Although the mechanism of action of amperozide is not entirely clear, both ritanserin and amperozide potently block binding of ligands to 5-HT_2 receptors [(15,21,36) and Table 2]. Further, amperozide interacts with DA receptors and DA reuptake sites only at much higher concentrations than at the 5-HT_2 binding site [(9,21) and Table 2]. For example, the affinity at the 5-HT_2 receptor site is about 25 nM, but the reported IC_{50}s for synaptosomal uptake of DA and 5-HT are 1.0 μM and 0.32 μM, respectively (9). Although the in vitro affinity of ritanserin is fivefold greater than amperozide, the difference in vivo may be much less (22). Consequently, it is unlikely that, at the doses used in the present study, amperozide would be present in a concentration sufficient to inhibit receptor sites other than the 5-HT_2 binding sites by more than 50%. Thus, a neurochemical combination of effects of amperozide serves to reduce the consumption of two rewarding substances of abuse: a depressant, represented by alcohol, and a stimulant, exemplified by cocaine.

Finally, earlier clinical trials of amperozide for the treatment of schizophrenia have revealed that this drug is not only well tolerated by the patient (1,2) but also does not produce extrapyramidal side effects. Clearly, therefore, amperozide may be a useful adjunct to the psychotherapy of both alcoholism (25) and substance abuse. If amperozide can reduce the craving for an abused substance, a patient may well remain in a program of therapy not only for a far longer interval but also with the greater likelihood of remaining drug free.

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