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Effects of cocaine and putative atypical antipsychotics on rat social behavior An ethopharmacological study

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Abstract

The effects of cocaine, amperozide, clozapine, olanzapine and cocaine/atypical antipsychotic combinations on aggression, affiliation and defensive behaviors was examined. Acute cocaine (30.0 mg/kg) decreased basal aggression and affiliation yet increased basal defense. Amperozide (1.0, 3.0 and 5.0 mg/kg) decreased basal aggression, affiliation and defense had no effect on the cocaine-induced decrease in affiliation, and accentuated the cocaine-induced decrease in aggression. Near basal levels of defense were observed for animals treated with either amperozide, clozapine (3.0 and 10.0 mg/kg but not 30.0 mg/kg) or olanzapine followed by cocaine. Clozapine (3.0, 10.0 and 30.0 mg/kg) decreased basal aggression and affiliation. Clozapine (30.0 mg/kg but not 3.0 or 10.0 mg/kg) decreased basal defense. Clozapine attenuated the cocaine-induced decrease in aggression. Although 3.0 and 10.0 mg/kg clozapine attenuated the cocaine-induced decrease in affiliation, 30.0 mg/kg clozapine accentuated this cocaine-induced effect. Olanzapine (1.0, 3.0 and 10.0 mg/kg) decreased basal aggression, affiliation and defense. Olanzapine had no effect on the cocaine-induced decrease in aggression. Olanzapine (3.0 mg/kg but not 1.0 or 10.0 mg/kg) attenuated the cocaine-induced decrease in affiliation. Thus, acute cocaine administration had an antiaggressive effect, suppressed affiliative behavior and enhanced defensive behavior. Amperozide, clozapine and olanzapine have anticonflict and anxiolytic effects, as well as potent and specific antiaggressive effects.

Keywords: Clozapine; Atypical antipsychotic; Cocaine; Aggression; Defense; Olanzapine; Social behavior; Amperozide; Affiliation

1. Introduction

Scientists have been searching for pharmacological treatments for a variety of behavioral, psychiatric and neurological problems including schizophrenia, social anxiety disorders, depression and addiction. Symptoms characteristic of schizophrenia fall into two broad categories—positive and negative. The positive symptoms of schizophrenia include distortions or exaggerations of inferential thinking (i.e., delusions), perception (i.e., hallucinations), language and communication (i.e., disorganized speech) and behavioral monitoring (i.e., grossly disorganized or catatonic behavior). The negative symptoms of schizophrenia include restrictions in the range and intensity of emotional expression (i.e., affective flattening), in the fluency and productivity of thought and speech (i.e., alogia), and in the initiation of goal-directed behavior (i.e., avolition). Social anxiety disorders are characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. And addictions are so varied they have to be described one class of drug at a time (e.g., alcohol, amphetamines and other sympathomimetics, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opiates, phencyclidine and sedatives, hypnotics or anxiolytics). Depression is also broken down into different subtypes (American Psychiatric Association, 1994).

One would not ordinarily think of classifying these different disease states together for the purpose of studying the effects of a single compound. These diseases all have different courses, age of onset and biological substrates. However, what these disease states have in common, along with many other psychiatric disturbances, is that they are

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psychological problems with neurobiological bases and with a social withdrawal component. Invariably animal models of these diseases are all characterized by a profound social withdrawal (Gambill and Kurnetsky, 1976; Heyne, 1996; Isovich et al., 2001; Kantor et al., 2000; Sams-Dodd, 1999; Schiorring, 1981). Therefore, finding a compound that addresses the social withdrawal component would be a useful adjunct therapy if not an effective treatment in and of itself. Furthermore, not only does cocaine reduce social interactions in both humans (Brower et al., 1988; Resnick and Resnick, 1984; Weddington, 1993) and animals (Darmani et al., 1990; Segal and Janowsky, 1978) but parallels to cocaine-induced behavioral aberrations in humans including social withdrawal, characterized by social isolation with no or inappropriate responses to social stimuli, have been consistently found in a variety of nonhuman animal species (Schiorring, 1981). Thus, animal models of cocaine-induced social withdrawal may be useful as behavioral assays for screening new pharmacological agents to treat a number of disease states including schizophrenia, social anxiety disorders, depression and addiction.

One purpose of the present experiments is to examine a compound that may be able to make a contribution to several different disease states because of its behavioral and pharmacological profile. The potent 5-HT_{2A} receptor antagonist and 5-HT uptake inhibitor, amperozide, was originally developed as a compound administered to pigs (*Sus serofa*) following regrouping to decrease aggression and physical damage (Björk et al., 1988; Gonyou et al., 1988). In animals, amperozide treatment leads to a suppression of food-reinforced behavior (Arolfo and McMillen, 1999; Egbe et al., 1990), inhibition of conditioned avoidance responding (ED_{50} = 4.2 mg/kg) (Egbe et al., 1990), blockade of amphetamine-induced hyperlocomotion and no effect on amphetamine-induced stereotypy (Egbe, 1989; Gustafsson and Christensson, 1990a). Amperozide does not produce catalepsy (Gustafsson and Christensson, 1990a) had minimal effects on vacuous jaw movements with chronic administration (Steinpreis et al., 1998) and had potent antiaggressive effects on social interactions (Björk et al., 1988; Gustafsson and Christensson, 1990b). Amperozide does not produce sedation even when administered at very high doses (ED_{50} > 50.0 mg/kg) (Gustafsson and Christensson, 1990b). Animal studies have indicated that amperozide reduced volitional alcohol consumption (McMillen et al., 1994; Myers et al., 1992), alcohol intake in a variety of alcohol-preferring rat strains (Lankford et al., 1996; Myers and Lankford, 1996; Myers et al., 1993a; Overstreet et al., 1997), operant responding for alcohol (Roberts et al., 1998), volitional cocaine intake (McMillen et al., 1993) and blocked the rewarding effects of cocaine as measured by the conditioned place preference paradigm (Jones and McMillen, 1995) without significantly affecting food intake, water intake, body weight or producing other adverse side effects. Amperozide's reduction of alcohol consumption is apparently irreversible (Myers et al., 1993b). Furthermore, animal studies have indicated that amperozide has antidepressant effects since amperozide inhibited mouse-killing (muricidal) behavior (ED_{50} = 0.16–2.6 mg/kg) and decreased the duration of immobility in a behavioral despair test. Amperozide seems to have anxiolytic effects since amperozide inhibited isolation-induced fighting (ED_{50} = 1.1–2.2 mg/kg) and increased punished responding in a conflict test (Gustafsson and Christensson, 1990b). Thus, amperozide may be a compound that can make contributions to multiple disease states, without risk of habit-forming (Rademacher et al., 2000), overdose or harmful and aversive side effects.

Previous research in our laboratory using a tether paradigm, in which the movement of one of two rats is restricted to one-half of an observation chamber via the use of a harness and flexible metal cord, has demonstrated that 20.0, 25.0 and 30.0 mg/kg doses of cocaine produce social withdrawal in rats. Additionally, 1.0, 3.0 and 5.0 mg/kg amperozide injections returned social interactions to near-control levels when co-administered with a 30.0 mg/kg cocaine dose. Amperozide administered alone increased social interactions to above baseline levels. Anecdotal written observations made by the observers indicated that amperozide seemed to induce affiliative behaviors in these rats (Rademacher et al., 1999). One disadvantage of using a tether paradigm is that social interactions cannot be broken down into subcategories (i.e., pins, mounts and grooming) because: (a) the tether could conceivably interfere with the proper execution of some of these behaviors and (b) in the condition in which the freely moving rat is drug-treated, this rat can and will escape from pins and mounts that would occur with the untreated, tethered rat. One advantage of a freely moving paradigm, which was selected for use in the present set of experiments, is that social interactions can be broken down into subcategories. The aim of the present set of experiments is to use the freely moving paradigm to obtain a global picture of the effects of cocaine, the putative atypical antipsychotics, amperozide, clozapine and olanzapine, as well as the effects of cocaine and atypical antipsychotic combinations on the number of aggressive, affiliative and defensive behaviors in rats (*Rattus norvegicus*).

Many of the behavioral effects of the atypical antipsychotic drug, clozapine, which has proven efficacy against both the positive and negative symptoms of schizophrenia, are similar to the behavioral effects of amperozide. Clozapine has dramatic antiaggressive effects in schizophrenic patients, which cannot be explained by sedation (Buckley, 1999; Buckley et al., 1995; Keck et al., 2000; Vesce et al., 2001; Volavka, 1999). Clozapine inhibited isolation-induced aggression in male mice (Sanchez et al., 1993) and administration of a novel antipsychotic compound that appears to have a clozapine-like profile, S18327, blocked aggression in isolated mice (Millan et al., 1998). Clozapine administration resulted in an inhibition of conditioned avoidance responding (Egbe et al., 1990) and an increase in punished responding in pigeons (Benvenga and Leander, 1995). Clozapine (1.25–5.0 mg/kg) administration decreased responding for

food maintained under a variable-interval 30 (VI 30) schedule of reinforcement and decreased responding for food and shock maintained under a fixed-ratio 10 (FR 10) schedule of reinforcement (Moore et al., 1994). These findings suggests that clozapine has anticonflict effects. Clozapine accentuated situation-appropriate approach behavior in mice (Dixon et al., 1994), reversed phencylclidine (PCP)-induced social withdrawal in rats (Corbett et al., 1995), and reversed the effects of PCP on specific social behaviors (e.g., side threats and mounting) (Steinpreis et al., 1994). Clozapine increased social interaction behaviors between pairs of unfamiliar rats. In the unfamiliar rat paradigm the novel rat is viewed as serving as an anxiogenic stimulus. This finding indicates that clozapine has anxiolytic effects (Corbett et al., 1993). Clozapine attenuated the rewarding effects of cocaine as measured by the conditioned place preference paradigm (Kosten and Nestler, 1994). In addition, clozapine and amperozide have similar binding profiles and physiological effects.

Many of the behavioral effects of the second generation antipsychotic drug, olanzapine, which has proven efficacy against the positive and negative symptoms of schizophrenia, are also similar to the behavioral effects of amperozide. Olanzapine (0.3125–1.25 mg/kg) administration decreased responding for food maintained under a VI 30 schedule of reinforcement and decreased responding for food and shock maintained under a FR 10 schedule of reinforcement (Moore et al., 1994). Intramuscular injections of olanzapine (0.01–1.0 mg/kg) increased punished responding at doses below those which had an effect on unpunished responding (Benvenga and Leander, 1995). These findings suggest that olanzapine has anticonflict effects. Olanzapine reduces the symptoms of agitation, hostility and aggression in schizophrenic patients (Bhana et al., 2001; Buckley, 1999; Keck et al., 2000; Vesce et al., 2001). Olanzapine reversed PCP-induced social withdrawal and PCP-induced stereotyped behaviors in rats (Corbett et al., 1993). Olanzapine attenuated the rewarding effects of cocaine as measured by the conditioned place preference paradigm (Meil and Schechter, 1997). In addition, olanzapine and amperozide have similar binding profiles and physiological effects.

When two freely moving untreated male rats are placed in a chamber together they tend to actively seek each other out and the animals remain in close proximity for long time periods. Usually, these social interactions between unrestrained and untreated male conspecifics are affiliative, characterized by nuzzling, sniffing and huddling (Ewer, 1968). Rat huddling behavior has been viewed as important for maintaining the cohesion of litters throughout early life, and it apparently remains a consistent feature of social behavior of the rat during adulthood (Schank and Alberts, 1997). However, at times, the social behavior of rats is characterized by aggressive behaviors (Cairns and Scholtz, 1973). The purpose of these experiments was to determine the effects of cocaine, amperozide, clozapine, olanzapine and cocaine/atypical antipsychotic combinations on specific social behaviors that can be characterized as aggressive, defensive or affiliative in same-sex conspecifics. The following hypotheses were tested in the present study: (a) acute cocaine (30.0 mg/kg) administration will decrease basal aggression and affiliation, yet will increase basal defense; (b) amperozide (1.0, 3.0 and 5.0 mg/kg), clozapine (3.0, 10.0 and 30.0 mg/kg) and olanzapine (1.0, 3.0 and 10.0 mg/kg) will dose-dependently decrease basal aggression and defense, yet will dose-dependently increase basal affiliation; and (c) amperozide, clozapine and olanzapine will accentuate the cocaine-induced decrease in aggression, attenuate the cocaine-induced decrease in affiliation and attenuate the cocaine-induced increase in defensive behavior.

2. Method

2.1. Animals

A total of 60 male albino Sprague–Dawley rats weighing between 300 and 350 g served as subjects for the first, second and third experiments (Harlan Sprague–Dawley, Indianapolis, IN). For each experiment, a total of 10 rats were drug-treated and a total of 10 rats were untreated conspecifics. All of the rats were housed individually in a colony room with an ambient temperature of 20 °C and a 12-h light/dark cycle (lights on at 0700 h). All observations were conducted during the lights on part of the cycle. Standard rat chow and water were available ad libitum.

2.2. Animal care

The experimental protocol was approved by the University of Wisconsin-Milwaukee Animal Care and Use Committee. All experiments were carried out in accordance with the Declaration of Helsinki and with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

2.3. Drugs

Amperozide (*N*-ethyl-4-[4′,4′-bis(ρ-flouro-phenyl)butyl]-1-piperazinecarboxamide) was donated by Kabi Pharmacia Therapeutics (Helsingborg, Sweden) and was dissolved in a 0.9% saline vehicle. The selection of the doses of amperozide (1.0, 3.0 and 5.0 mg/kg) used was based on previous research in our laboratory indicating that acute amperozide administration reverses cocaine-induced social withdrawal (Rademacher et al., 1999) and promotes social cohesion between pairs of unfamiliar male rats (Rademacher et al., 2002). Clozapine was purchased from Sandoz Pharmaceutical (St. Louis, MO) and was dissolved in a 0.3% tartaric acid vehicle. Olanzapine (2-methyl-10-(4-methyl-1-piperazinyl)-4*H*-thieno[2,3-*b*][1,5]-benzodiazapine) was purchased from Eli Lilly Laboratories (Indianapolis, IN) and was dissolved in a 0.9% saline vehicle. The selection of the

doses of olanzapine (1.0, 3.0 and 10.0 mg/kg) and clozapine (3.0, 10.0 and 30.0 mg/kg) to be used was based on a previous study conducted in our laboratory which investigated the effects of these compounds on locomotion and balance as assessed by rotorod performance (Steinpreis et al., 1999). Cocaine hydrochloride was donated by the National Institute on Drug Abuse (Bethesda, MD) and was dissolved in a 0.9% saline vehicle. A 30.0-mg/kg dose of cocaine was used since it produces social withdrawal in the rat (Rademacher et al., 1999, 2002).

2.4. Apparatus

The observation chamber consisted of a rectangular box ($110 \times 32 \times 44$ cm) with three wooden walls, one Plexiglas wall and a wire mesh floor.

2.5. Behaviors indicative of aggression

The following aggressive behaviors, adapted from the literature (Grant, 1963; Grant and MacKintosh, 1963), were recorded: (a) lateral threatening, which has been operationally defined as an arched-back posture oriented towards and often includes shoving the other rat, and (b) crawling under which has been defined as a pushing of the head and forepart of the body beneath the other rat. The incidences of lateral threatening and crawling under were recorded and summed to produce a total aggression score (Taylor, 1976).

2.6. Defensive behavior

The following defensive behaviors were also taken from the literature (Albonetti and Farabollini, 1993; Albonetti et al., 1996; Grant, 1963; Grant and MacKintosh, 1963): (a) lateral defense, in which the animal exposes its flank to the conspecific. The foreleg facing the conspecific and the head are withdrawn; (b) upright defense, in which the rat exposes its belly to the conspecific in a half-erect posture; and (c) retreating has been defined simply as when the rat moves away from the conspecific. Incidences of lateral defense, upright defense and retreating were recorded and summed to produce a total defensive score.

2.7. Behaviors indicative of affiliation

The following affiliative behaviors were adapted from the literature (Albonetti and Farabollini, 1993; Albonetti et al., 1996; Grant, 1963; Grant and MacKintosh, 1963): (a) attending, in which the animal orients its head, ears and possibly the whole body toward the conspecific; (b) approaching, during which the animal moves toward the conspecific; (c) investigating has been defined as sniffing the conspecific's body, excluding the ano-genital area; and (d) ano-genital sniffing has been defined as sniffing the conspecific's ano-genital region. Incidences of attending, approaching, investigating and ano-genital sniffing were recorded and summed to produce a total affiliation score (Albonetti and Farabollini, 1993; Albonetti et al., 1996).

2.8. Procedure

In all three experiments, both rats were freely moving at all times. The dose of cocaine was held constant throughout. There were eight drug conditions in the first and third experiments and nine drug conditions in the second experiment. In all three experiments, all injections were intraperitoneal and the drug-treated animals were given either one of the eight or one of the nine drug combinations once each week in accordance with a Latin square design. Only one rat in each pair ever received any drug. In other words, untreated conspecifics did not subsequently serve as drug-treated animals. The drug-treated rats were placed with a different untreated conspecific for either each of the eight or each of the nine observations. In all three experiments, on test days, drug-treated rats received two intraperitoneal injections. In the first experiment, the first injection was either saline or amperozide. One hour later, these same rats received a second injection (either saline or 30.0 mg/kg cocaine). In the second experiment, the first injection was either tartaric acid, saline or clozapine. One hour later, these same rats received a second injection (either tartaric acid, saline or 30.0 mg/kg cocaine). In the third experiment, the first injection was either saline or olanzapine. One hour later, these same rats received a second injection (either saline or 30.0 mg/kg cocaine). For all experiments, immediately after the second injection, the drug-treated rat was marked with nontoxic magic marker to promote observer identification and was placed at the opposite end of the observation chamber relative to an untreated conspecific stimulus rat. The rats' social behavior was videotaped via a camcorder (Model SK-F100, Toshiba, Tokyo, Japan) for 20 min. Later, two trained observers, blind to the drug and dose received, reviewed the videotaped sessions and recorded incidences of specific social behaviors.

2.9. Statistical analysis

Repeated-measures analysis of variance (ANOVA) was used to determine if there was a significant change in the number of behaviors classified as aggressive, defensive or affiliative. Post-hoc Tukey's HSD comparisons were used to determine if there was a significant change in the incidence of each class of behavior relative to either the control condition or the cocaine only condition. An α level of .05 was used for all statistical tests.

3. Results

3.1. Experiment 1

Repeated-measures ANOVA revealed a main effect for incidence of behavior, $F(2,144) = 317.660$, $P < .001$, a main

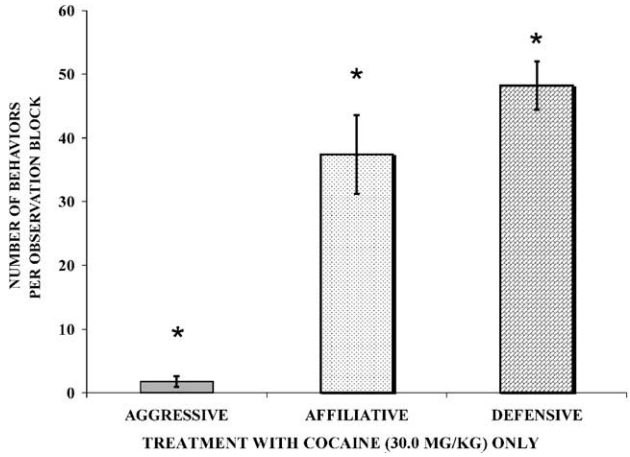

Fig. 1. Acute administration of cocaine (30.0 mg/kg) decreased the basal level of aggression and affiliation, and increased the basal level of defensive behavior: * $P < .01$, Tukey's HSD comparisons.

effect for treatment condition, $F(7,72) = 6.315$, $P < .001$, and a significant interaction, $F(14,144) = 7.901$, $P < .001$. Post-hoc Tukey's HSD comparisons revealed that acute cocaine (30.0 mg/kg) administration decreased the basal level of aggression and affiliation yet increased the basal level of defensive behavior (P's $< .01$). Amperozide (1.0, 3.0 and 5.0 mg/kg) pretreatment decreased the basal level of aggression (P's $< .01$) and defensive behavior (P's $< .01$). Pretreatment with 3.0 and 5.0 mg/kg amperozide (P's $< .01$) but not 1.0 mg/kg amperozide ($P > .05$) decreased the basal level of affiliation. Amperozide (1.0, 3.0 and 5.0 mg/kg) accentuated the cocaine-induced decrease in aggression (P's $< .01$). Amperozide (1.0, 3.0 and 5.0 mg/kg) had no effect on the cocaine-induced decrease in affiliation (P's $> .05$). Near basal levels of defensive behavior were observed for animals that were treated with amperozide (1.0, 3.0 and 5.0 mg/kg) followed by cocaine (P's $> .05$). These data are illustrated in Figs. 1–7.

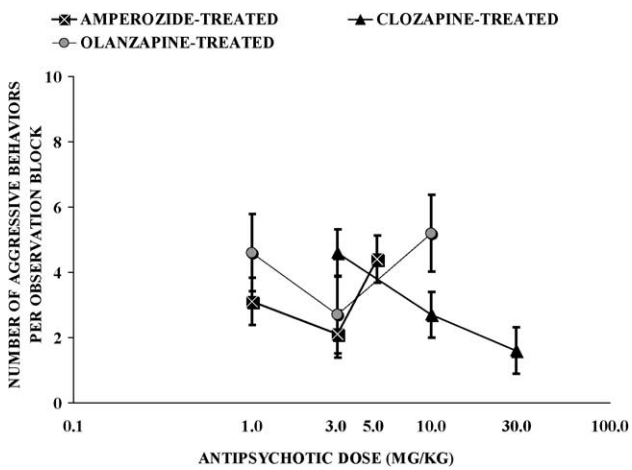

Fig. 2. Amperozide (1.0, 3.0 and 5.0 mg/kg), clozapine (3.0, 10.0 and 30.0 mg/kg) and olanzapine (1.0, 3.0 and 10.0 mg/kg) decreased the basal level of aggression.

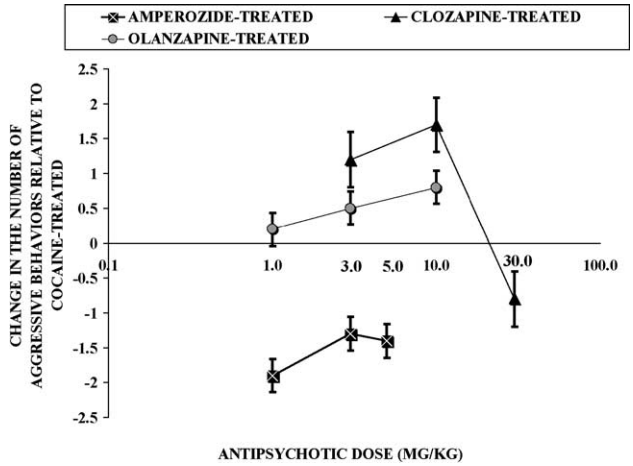

Fig. 3. A significant decrease in the level of aggression induced by a high dose of cocaine (30.0 mg/kg) was attenuated by 3.0 and 10.0 mg/kg but not 30.0 mg/kg clozapine. Amperozide (1.0, 3.0 and 5.0 mg/kg) accentuated the cocaine-induced decrease in the number of aggressive behaviors. Olanzapine (1.0, 3.0 and 10.0 mg/kg) had no effect on the cocaine-induced decrease in the level of aggression.

3.2. Experiment 2

Repeated-measures ANOVA revealed a main effect for incidence of behavior, $F(2,162) = 728.835$, $P < .001$, a main effect for treatment condition, $F(8,81) = 20.531$, $P < .001$, and a significant interaction, $F(16,162) = 17.790$, $P < .001$. Post-hoc Tukey's HSD comparisons revealed that acute cocaine (30.0 mg/kg) administration decreased the basal level of aggression and affiliation yet increased the basal level of defensive behavior (P's $< .01$). Clozapine (3.0, 10.0 and 30.0 mg/kg) pretreatment decreased the basal level of aggression (P's $< .01$). Pretreatment with 10.0 and 30.0 mg/kg clozapine (P's $< .01$) but not 3.0 mg/kg clozapine ($P > .05$)

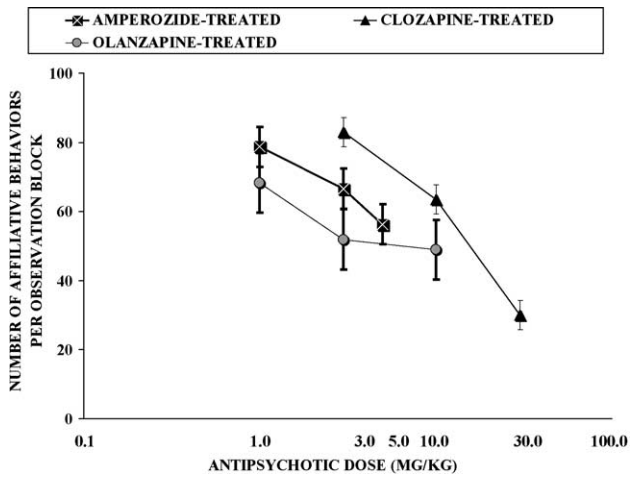

Fig. 4. Amperozide (3.0 and 5.0 mg/kg but not 1.0 mg/kg), clozapine (10.0 and 30.0 mg/kg but not 3.0 mg/kg) and olanzapine (1.0, 3.0 and 10.0 mg/kg) decreased the basal level of affiliation.

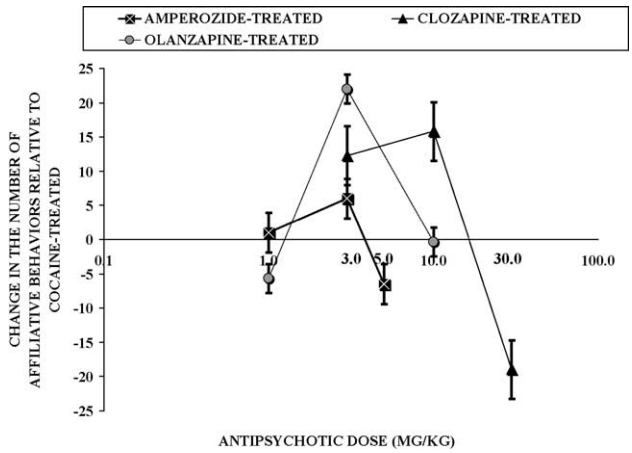

Fig. 5. The effects of amperozide, clozapine and olanzapine on a cocaine-induced decrease in the level of affiliation. Amperozide (1.0, 3.0 and 5.0 mg/kg) and olanzapine (1.0 and 10.0 mg/kg) had no effect on a decrease in affiliation induced by a high dose of cocaine (30.0 mg/kg). A cocaine-induced decrease in the level of affiliation was attenuated by 3.0 and 10.0 mg/kg clozapine and 3.0 mg/kg olanzapine. A cocaine-induced decrease in the level of affiliation was accentuated by 30.0 mg/kg clozapine.

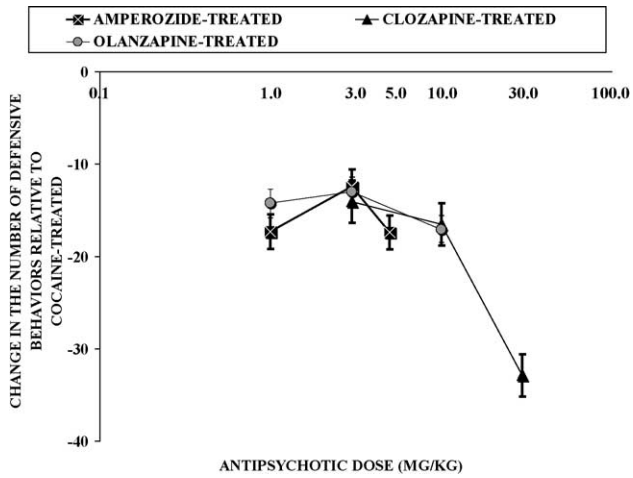

Fig. 7. Effects of amperozide, clozapine and olanzapine on a cocaine-induced increase in the number of defensive behaviors. Near baseline levels of defensive behaviors were observed for animals treated with either amperozide (1.0, 3.0 and 5.0 mg/kg), clozapine (3.0 and 10.0 mg/kg but not 30.0 mg/kg) or olanzapine (1.0, 3.0 and 10.0 mg/kg) followed by 30.0 mg/kg cocaine.

decreased the basal level of affiliation. Pretreatment with 30.0 mg/kg clozapine ($P<.01$) but not 3.0 or 10.0 mg/kg clozapine (P's>.05) decreased the basal level of defensive behavior. The cocaine-induced decrease in aggression was attenuated by 3.0 and 10.0 mg/kg clozapine (P's>.05) but not 30.0 mg/kg clozapine ($P<.01$). The cocaine-induced decrease in affiliation was attenuated by 3.0 and 10.0 clozapine (P's>.05) yet accentuated by 30.0 mg/kg clozapine ($P<.01$). Near basal levels of defensive behavior were observed for animals that were treated with 3.0 and 10.0 mg/kg clozapine (P's>.05) but not 30.0 mg/kg clozapine ($P>.01$) followed by cocaine. These data are illustrated in Figs. 1–7.

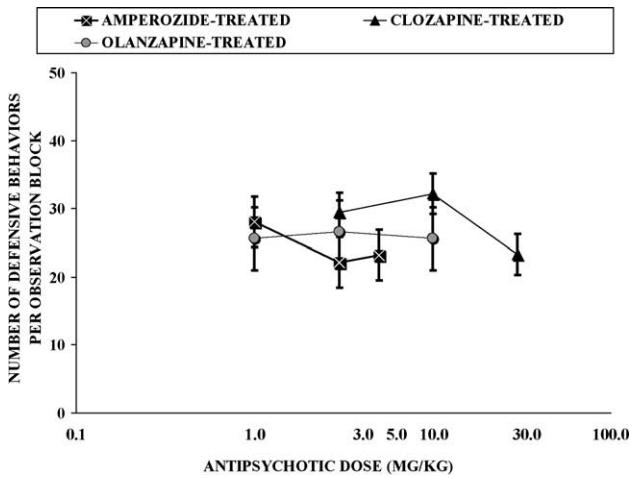

Fig. 6. Amperozide (1.0, 3.0 and 5.0 mg/kg), clozapine (30.0 mg/kg but not 3.0 and 10.0 mg/kg) and olanzapine (1.0, 3.0 and 10.0 mg/kg) decreased the basal level of defensive behaviors.

3.3. Experiment 3

Repeated-measures ANOVA revealed a main effect for incidence of behavior, $F(2,144)=174.424$, $P<.001$, a main effect for treatment condition, $F(7,72)=2.540$, $P<.05$, and a significant interaction, $F(14,144)=4.242$, $P<.001$. Post-hoc Tukey's HSD comparisons revealed that acute cocaine (30.0 mg/kg) administration decreased the basal level of aggression and affiliation yet increased the basal level of defensive behavior (P's<.01). Olanzapine (1.0, 3.0 and 10.0 mg/kg) pretreatment decreased the basal level of aggression, affiliation and defensive behavior (P's<.01). Olanzapine (1.0, 3.0 and 10.0 mg/kg) had no effect on the cocaine-induced decrease in aggression (P's>0.05). Treatment with 3.0 mg/kg olanzapine attenuated the cocaine-induced decrease in affiliative behaviors ($P>.05$). Treatment with 1.0 and 10.0 mg/kg olanzapine had no effect on the cocaine induced-decrease in affiliation (P's>.05). Near baseline levels of defensive behavior were observed for animals that were treated with olanzapine (1.0, 3.0 and 10.0 mg/kg) followed by cocaine (P's>.05). These data are illustrated in Figs. 1–7.

4. General discussion

Administration of 30.0 mg/kg cocaine decreased the basal level of aggression. This result is consistent with the finding that cocaine administration resulted in a dose-dependent decrease in intruder-evoked aggression in isolated and non-isolated mice (Miczek and O'Donnell, 1978). The atypical antipsychotics, amperozide, clozapine and olanzapine, decreased the basal level of aggression. The finding that

amperozide decreased the basal level of aggression and accentuated a cocaine-induced decrease in aggression is consistent with the finding that amperozide had a potent inhibitory effect on muricidal behavior, exerted an inhibitory effect on fighting between pairs of isolated mice (Gustafsson and Christensson, 1990b) and resulted in a potent antiaggressive effect on pig social behavior (Björk et al., 1988; Gonyou et al., 1988). The finding that clozapine and olanzapine decreased the basal level of aggression and olanzapine had no effect on the cocaine-induced decrease in aggression is consistent with specific antiaggressive effects with minimal motor impairment reported in animals (Garmendia et al., 1992; Rewerski et al., 1979) and humans (Bhana et al., 2001; Buckley, 1999; Buckley et al., 1995; Fava, 1997; Keck et al., 2000; Ratey et al., 1993; Vesce et al., 2001). The finding that 3.0 and 10.0 mg/kg but not 30.0 mg/kg clozapine attenuated the cocaine-induced decrease in aggression is consistent with the findings of others. Clozapine inhibited isolation-induced aggression in male mice (Sanchez et al., 1993) and Dixon et al. (1994) reported that clozapine administered to presumably nonaggresive mice later exposed to aggressive conspecifics resulted in increased levels of aggression in the clozapine-treated mice. Based on the results of Dixon et al. (1994), we predict that clozapine administered to aggressive mice later exposed to a nonaggressive conspecific would result in decreased levels of aggression in the clozapine-treated mice. However, we hypothesize that clozapine administered to aggressive mice later exposed to a nonaggressive conspecific would result in decreased levels of aggression in the clozapine-treated mice. Thus, we hypothesize that the effects of clozapine on aggression are dose-dependent, which is supported by our results, as well as context-dependent.

Acute cocaine (30.0 mg/kg) administration significantly decreased the number of affliative behaviors. This finding is consistent with a report of a cocaine-mediated suppression of social affiliative behaviors in monkeys (*Macuca fascata*) (Crowley et al., 1992). Administration of amperozide (3.0 and 5.0 mg/kg but not 1.0 mg/kg), clozapine (10.0 and 30.0 mg/kg but not 3.0 mg/kg) and olanzapine decreased the basal level of affiliation. Amperozide and 1.0 and olanzapine (1.0 and 10.0 mg/kg) had no effect on the cocaine-induced decrease in affiliation. Although 3.0 and 10.0 mg/kg clozapine and 3.0 mg/kg olanzapine attenuated the cocaine-induced decrease in affiliation, 30.0 mg/kg clozapine accentuated this cocaine-induced effect. In this free moving paradigm, the novel (i.e., unfamiliar) rat is viewed as serving as an anxiogenic stimulus (Corbett et al., 1993). Thus, the findings that administration of 3.0 and 10.0 mg/kg clozapine and 3.0 mg/kg olanzapine attenuated the cocaine-induced decrease in affiliation is consistent with the findings that clozapine and olanzapine have anticonflict and anxiolytic effects (Benvenga and Leander, 1995; Corbett et al., 1993; Moore et al., 1994). However, near baseline levels of affiliation were not observed regardless of the dose of atypical antipsychotic administered. Given that the presence of an unfamiliar (novel) conspecific rat serves as an anxiogenic stimulus (Corbett et al., 1993) and cocaine is also an anxiogenic stimulus (Crowley et al., 1992; Geracioti and Post, 1991), it is hypothesized that these two conditions acted synergistically rather than additively to produce a level of social withdrawal with a marked decrease in the number of affiliative behaviors that the antipsychotic compounds, amperozide, clozapine and olanzapine, were unable to overcome.

Acute cocaine (30.0 mg/kg) administration significantly increased the number of defensive behaviors. A cocaine-induced increase in basal defensive behaviors is consistent with reports that acute cocaine administration enhanced a number of defensive behaviors, including flight and escape (Blanchard and Blanchard, 1999; Herbert et al., 1999). For instance, intravenous administration of cocaine resulted in an initial flight response that peaked at approximately 5 min postinfusion and declined significantly by 15 min postinfusion. However, heightened defensiveness, as measured by avoidance, escape, immobility and upright defense, persisted for at least 30 min, suggesting prolonged, residual effects of cocaine on a variety of defensive behaviors (Herbert et al., 1999). Although the underlying mechanism for the effect of cocaine on defensive behavior is not known, there is some evidence suggesting that activation of the hypothalamus–pituitary–adrenal (HPA) axis is necessary for the development of cocaine-induced stereotypy in rats (Marinelli et al., 1997; Prather and Lal, 1992). Thus, it is possible that circulating corticosteroids may have played a permissive role in the cocaine-induced increase in the number of defensive behaviors observed.

The finding that cocaine administration resulted in an increase in the number of defensive behaviors is consistent with clinical reports of panic and anxiety associated with cocaine use in humans (Crowley et al., 1992; Geracioti and Post, 1991). Results of preclinical pharmacological studies suggest that flight and escape responses may be useful indicators of panic. For instance, panicogenic compounds such as yohimbine selectively potentiate flight and escape behaviors in mice (Blanchard et al., 1993), whereas panicolytic drugs reduce flight and escape behavior in mice (Griebel et al., 1995a,b). Additionally, cocaine administration resulted in an initial flight response that had a sudden onset but was short-lasting. Thus, the temporal characteristics of the flight response parallel those of panic/anxiety attacks in humans. The longer lasting increases in other less intense defensive behaviors suggests a period of residual hyperdefensiveness following the peak "panic" episodes, which is typical of residual anxiety following panic attacks in humans (Herbert et al., 1999). Therefore, the present findings are consistent with the view that acute cocaine administration has potent effects on defensive behaviors in rats and that these effects may be related to cocaine-associated panic and/or anxiety-related disorders in humans.

It is proposed that the cocaine-induced increase in the number of defensive behaviors is, in fact, due to cocaine, at

this dose, acting as an anxiogenic/panicogenic stimulus. The finding that near baseline levels of defensive behaviors were observed for animals treated with either amperozide, clozapine (3.0 and 10.0 mg/kg but not 30.0 mg/kg) or olanzapine followed by cocaine is consistent with reports that amperozide, clozapine and olanzapine have anticonflict and anxiolytic effects. Hence, these findings are consistent with the report that amperozide exerted an inhibitory effect on fighting between pairs of isolated mice, increased punished responding in Vogel's conflict test and increased the time spent in the open arms in Vogel's elevated plus maze (Engel et al., 1986, 1989). Moreover, these findings are consistent with the report that both clozapine and olanzapine decreased responding for food maintained under a VI 30 schedule of reinforcement and decreased responding for food and shock maintained under a FR 10 schedule of reinforcement (Moore et al., 1994) as well as the report that clozapine and olanzapine administration resulted in an increase in punished responding (Benvenga and Leander, 1995).

In summary, acute cocaine administration resulted in decreases in the number of aggressive and affiliative behaviors and increases in the number of defensive behaviors. The latter finding is consistent with clinical reports of panic and anxiety associated with cocaine use in humans. It is possible that circulating corticosteroids may have played a permissive role in the cocaine-induced increase in the number of defensive behaviors observed. Amperozide, clozapine and olanzapine decreased the basal level of aggression. This finding is consistent with reports of specific antiaggressive effects of these compounds in animal models, as well as in humans. Whereas olanzapine had no effect on a cocaine-induced decrease in aggression, amperozide accentuated this cocaine-induced effect and clozapine (3.0 and 10.0 mg/kg but not 30.0 mg/kg) attenuated the cocaine-induced decrease in aggression. We hypothesize that clozapine has dose-and context-dependent effects on aggression. Despite the fact that 10.0 and 30.0 mg/kg clozapine and 3.0 mg/kg olanzapine attenuated the cocaine-induced decrease in affiliative behaviors, near baseline levels of affiliation were not observed regardless of the dose of atypical antipsychotic administered. Given that the presence of an unfamiliar (novel) conspecific rat serves as an anxiogenic stimulus and cocaine is also an anxiogenic stimulus, it is hypothesized that these two conditions acted synergistically rather than additively to produce a level of social withdrawal with a marked decrease in the number of affiliative behaviors that the antipsychotic compounds, amperozide, clozapine and olanzapine, were unable to overcome. The finding that near baseline levels of defensive behaviors were observed for animals treated with either amperozide, clozapine (3.0 and 10.0 mg/kg but not 30.0 mg/kg) or olanzapine followed by cocaine is consistent with reports that amperozide, clozapine and olanzapine have anticonflict and anxiolytic effects. Thus, acute administration of a high dose of cocaine (30.0 mg/kg) had an antiaggressive effect, supressed affiliative behavior and enhanced defensive behavior perhaps due to its panicogenic and anxiogenic effects. The results of the present study contribute to the body of evidence suggesting that amperozide, clozapine and olanzapine have anxiolytic and anticonflict effects, as well as potent and specific antiaggressive effects. The results of the present study, when taken in combination with the existing literature, suggest that amperozide, clozapine and olanzapine are perhaps best viewed as multipurpose compounds that may be able to make contributions to multiple disease states that included marked social withdrawal including schizophrenia, social anxiety disorder, depression and addiction, without risk of habit-forming, overdose or harmful and aversive side effects.

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References

Albonetti ME, Farabollini F. Effects of single and repeated restraint on the social behavior of rats. Physiol Behav 1993;53:937–42.

Albonetti E, González MI, Siddiqui A, Wilson CA, Farabollini F. Involvement of the 5-HT_{1A} subtype receptor in the neonatal organization of agonistic behaviour in the rat. Pharmacol, Biochem Behav 1996;54:189–93.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.

Arolfo MP, McMillen BA. Effects of amperozide and tiospirone, atypical antipsychotic 5-HT_2 drugs, on food-reinforced behavior in rats. Physiol Behav 1999;68:93–8.

Benvenga MJ, Leander JD. Olanzapine, an atypical antipsychotic, increases rates of punished responding in pigeons. Psychopharmacology 1995;119:133–8.

Bhana N, Foster RH, Olney R, Plosker GL. Olanzapine: an updated review of its use in the management of schizophrenia. Drugs 2001;61:111–61.

Björk A, Olsson NG, Christensson E, Martinsson K, Olsson O. Effects of amperozide on biting behavior and performance in restricted-fed pigs following regrouping. J Anim Sci 1988;66:669–75.

Blanchard DC, Blanchard RJ. Cocaine potentiates defensive behaviors related to fear and anxiety. Neurosci Biobehav Rev 1999;23:981–91.

Blanchard RJ, Taukulus HK, Rodgers RJ, Magee LK, Blanchard DC. Yohimbine potentiates active defensive responses to threatening stimuli in Swiss–Webster mice. Pharmacol, Biochem Behav 1993;44:673–81.

Brower KJ, Maddahian E, Blow P, Deresford TP. A comparison of self-reported symptoms and DSMIII-R criteria for cocaine withdrawal. Am J Drug Alcohol Abuse 1988;14:347–56.

Buckley PF. The role of typical and atypical antipsychotic medications in the management of agitation and aggression. J Clin Psychiatry 1999;60:52–60.

Buckley P, Bartell J, Donenwirth K, Lee S, Torigoe F, Schulz SC. Violence and schizophrenia: clozapine as a specific antiaggressive agent. Bull Am Acad Psychiatry Law 1995;23:607–11.

Cairns RB, Scholtz SD. Fighting in mice: dyadic escalation and what is learned. J Comp Physiol Psychol 1973;85:540–50.

Corbett R, Hartman H, Kerman LL, Woods AT, Strupczewski JT, Helsley GC, Conway PC, Dunn RW. Effects of atypical antipsychotic agents on social behavior in rodents. Pharmacol, Biochem Behav 1993;45:9–17.

Corbett R, Camacho F, Woods AT, Kerman LL, Fishkin RJ, Brooks K, Dunn RW. Antipsychotic agents antagonize non-competitive *N*-methyl-D-aspartate antagonist-induced behaviors. Psychopharmacology 1995;120:67–74.

Crowley TJ, Mikulich SK, Williams EA, Zerbe GO, Ingersoll NC. Cocaine, social behavior, and alcohol-solution drinking in monkeys. Drug Alcohol Depend 1992;29:205–23.

Darmani NA, Hadfield MG, Carter WH, Martin BR. Acute and chronic effects of cocaine on isolation-induced aggression in mice. Psychopharmacology 1990;102:37–40.

Dixon AK, Huber C, Lowe DA. Clozapine promotes approach-oriented behavior in male mice. J Clin Psychiatry 1994;55:4–7.

Egbe PC. Locomotor effects of amperozide: antagonism of amphetamine-induced locomotor stimulation. Arzneimittelforschung 1989;39: 1223–4.

Egbe P, Engel J, Gustafsson B, Christensson E. Amperozide and conditioned behavior in rats: potentiation by classic neuroleptics and α-methylparatyrosine. Pharmacol Toxicol 1990;66:18–21.

Engel JA, Egbe P, Liljequist S. Collegium internationale neuropsycho-pharmacologium. San Juan, Puerto Rico, 1986;129.

Engel JA, Egbe P, Liljequist S, Söderpalm B. Effects of amperozide in two models of anxiety. Pharmacol Toxicol 1989;64:429–33.

Ewer RF. Ethology of mammals. New York: Plenum, 1968.

Fava M. Psychopharmacological treatment of pathological aggression. Psychiatr Clin North Am 1997;20:427–51.

Gambill JD, Kurnetsky C. Effects of chronic d-amphetamine on social behavior of the rat: implications for an animal model of paranoid schizophrenia. Psychopharmacology 1976;50:215–23.

Garmendia L, Sanchez JR, Azpiroz A, Brain PF, Simon VM. Clozapine: strong antiaggressive effects with minimal motor impairment. Physiol Behav 1992;51:51–4.

Geracioti TD, Post RM. Onset of panic disorder associated with rare use of cocaine. Biol Psychiatry 1991;29:403–6.

Gonyou HW, Parafet KA, Anderson DB, Olson RD. Effects of amperozide on aggression and productivity on growing-finishing pigs. J Anim Sci 1988;66:2856–64.

Grant EC. An analysis of the social behaviour of the male laboratory rat. Behav 1963;21:261–81.

Grant EC, MacKintosh JH. A comparison of the social postures of some common laboratory rodents. Behav 1963;21:246–59.

Griebel G, Blanchard DC, Agnes R, Blanchard RJ. Differential modulation of antipredator defensive behavior in Swiss–Webster mice following acute and chronic treatment with imipramine and fluozetine. Psychopharmacology 1995a;120:57–66.

Griebel G, Blanchard DC, Jung A, Lee J, Masuda CK, Blanchard RJ. Further evidence that the mouse defense test battery is useful for screening anxiolytic and panicolytic drugs: effects of acute and chronic treatment with alprazolam. Neuropharmacology 1995b;34:1625–33.

Gustafsson B, Christensson E. Amperozide—a new putatively antipsychotic drug with a limbic mode of action on dopamine mediated behaviors. Pharmacol Toxicol 1990a;66:34–9.

Gustafsson B, Christensson E. Amperozide and emotional behavior. Pharmacol Toxicol 1990b;66:34–9.

Herbert MA, Blanchard DC, Blanchard RJ. Intravenous cocaine precipitates panic-like flight responses and lasting hyperdefensiveness in laboratory rats. Pharmacol, Biochem Behav 1999;63:349–60.

Heyne A. The development of opiate addiction in the rat. Pharmacol, Biochem Behav 1996;53:11–25.

Isovich E, Engelmann M, Langraf R, Fuchs E. Social isolation after a single defeat reduces striatal dopamine transporter binding in rats. Eur J Neurosci 2001;13:1254–6.

Jones EA, McMillen BA. Amperozide attenuates the reinforcing effects of cocaine in the conditioned place preference paradigm. Pharm Sci 1995;1:471–4.

Kantor S, Anheuer ZE, Bagdy G. High social anxiety and low aggression in Fawn–Hooded rats. Physiol Behav 2000;71:551–7.

Keck PE, Strakowski SM, McElroy SL. The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. J Clin Psychiatry 2000;61:4–9.

Kosten TA, Nestler EJ. Clozapine attenuates cocaine conditioned place preference. Life Sci 1994;55:PL 9–14.

Lankford MF, Björk AK, Myers RD. Differential efficacy of serotonergic compounds in reducing alcohol drinking in P rats. Alcohol 1996;13: 399–404.

Marinelli M, Rouge-Pont F, De Jesus-Oliveira C, Le Moal M, Piazza PV. Acute blockade of corticosterone secretion decreases the psychomotor stimulant effects of cocaine. Neuropsychopharmacology 1997;16: 156–61.

McMillen BA, Jones EA, Hill LJ, Williams HL, Björk A, Myers RD. Amperozide, a 5-HT_2 antagonist, attenuates craving for cocaine by rats. Pharmacol, Biochem Behav 1993;46:125–9.

McMillen BA, Walter S, Williams HL, Myers RD. Comparison of the action of the 5-HT_2 antagonists amperozide and trazodone on preference for alcohol in rats. Alcohol 1994;11:203–6.

Meil WM, Schechter MD. Olanzapine attenuates the reinforcing effects of cocaine. Eur J Pharmacol 1997;340:17–26.

Miczek KA, O'Donnell JM. Intruder-evoked aggression in isolated and nonisolated mice: effects of psychomotor stimulants and L-DOPA. Psychopharmacology 1978;57:47–55.

Millan MJ, Gobert A, Newman-Tancredi A, Audinot V, Lejeune F, Rivet J, Cussac D, Nicolas J, Muller O, Lavielle G. S 16924 ((*R*)-2-{1-[2-(2,3-dihydro-benzo[1,4] dioxin-5-yloxy)-ethyl]-pyrrolidin-3yl}-1-(4-flourophenyl)-ethanone), a novel, potential antipsychotic with marked serotonin (5-$HT)_{1A}$ agonist properties: I. Receptorial and neurochemical profile in comparison with clozapine and haloperidol. J Pharmacol Exp Ther 1998;286:1341–55.

Moore NA, Rees GG, Sanger GG, Tye NC. Effects of olanzapine and other antipsychotic agents on responding maintained by a conflict schedule. Behav Pharmacol 1994;5:196–202.

Myers RD, Lankford MF. Suppression of alcohol preference in high alcohol drinking rats: efficacy of amperozide versus naltrexone. Neuropsychopharmacology 1996;14:139–49.

Myers RD, Lankford M, Björk A. Selective reduction by the 5-HT antagonist amperozide of alcohol preference induced in rats by systemic cyanamide. Pharmacol, Biochem Behav 1992;3:661–7.

Myers RD, Lankford M, Björk A. 5-HT_2 receptor blockade by amperozide suppresses ethanol drinking in genetically preferring rats. Pharmacol, Biochem Behav 1993a;45:741–7.

Myers RD, Lankford M, Björk A. Irreversible suppression of alcohol drinking in cyanamide-treated rats after sustained delivery of the 5-HT_2 antagonist amperozide. Alcohol 1993b;10:117–25.

Overstreet DH, McArthur RA, Rezvani AH, Post C. Selective inhibition of alcohol intake in diverse alcohol-preferring rat strains by the 5-HT_{2A} antagonist amperozide and FG 5974. Alcohol: Clin Exp Res 1997;21: 1448–54.

Prather PL, Lal H. Protracted withdrawal: sensitization of the anxiogenic response to cocaine in rats concurrently treated with ethanol. Neuropsychopharmacology 1992;623–9.

Rademacher DJ, Kuppinger HE, Thompson KJ, Harrington A, Kaczmarek HJ, Kopish AJ, Steinpreis RE. The effects of amperozide on cocaine-induced social withdrawal in rats. Behav Brain Res 1999;99:75–80.

Rademacher DJ, Anders KA, Riley MG, Nesbitt JT, Steinpreis RE. Determination of the place conditioning and locomotor effects of amperozide in rats: a comparison with cocaine. Exp Clin Psychopharmacol 2000;8: 434–43.

Rademacher DJ, Anderson AP, Steinpreis RE. Acute effects of amperozide and paroxetine on social cohesion in male conspecifics. Brain Res Bull 2002;58:187–91.

Ratey JJ, Leveroni C, Kilmer D, Gutheil C, Swartz B. The effects on clozapine on severely aggressive psychiatric inpatients in a state hospital. J Clin Psychiatry 1993;54:219–23.

Resnick RB, Resnick EB. Cocaine abuse and its treatment. Psychiatr Clin North Am 1984;7:713–28.

Rewerski W, Kostowski W, Piechocki T. Effects of some neuroleptic drugs on aggressive behavior in isolated mice. Acta Physiol Pol 1979;30: 295–8.

Roberts AJ, McArthur RA, Hull EE, Post C, Koob GF. Effects of amperozide, 8-OH-DPAT, and FG 5974 on operant responding for ethanol. Psychopharmacology 1998;137:25–32.

Sams-Dodd F. Phencyclidine in the social interaction test: an animal model of schizophrenia with face and predictive validity. Rev Neurosci 1999; 10:50–9.

Sanchez C, Arnt J, Hyttel J, Moltzen EK. The role of serotonergic mechanisms in inhibition of isolation-induced aggression in male mice. Psychopharmacology 1993;1–2:53–9.

Schank JC, Alberts JR. Self-organized huddles of rat pups modeled by simple rules of individual behavior. J Theor Biol 1997;189:11–25.

Schiorring E. Psychopathology induced by ''speed drugs''. Pharmacol, Biochem Behav 1981;14:109–12.

Segal DS, Janowsky DS. Psychostimulant-induced behavioral effects: possible models of schizophrenia. In: Lipton MA, DiMascio A, Killam KF, editors. Psychopharmacology: a generation of progress. New York: Raven Press, 1978. p. 1113–23.

Steinpreis RE, Sokolowski JD, Papanikolaou A, Salamone JD. The effects of haloperidol and clozapine on PCP- and amphetamine-induced suppression of social behavior in the rat. Pharmacol, Biochem Behav 1994; 47:579–85.

Steinpreis RE, Moser L, Parret F, Rutell E, Panos J. The effects of the atypical antipsychotic amperozide on vacuous jaw movements in rats: a novel dose response profile. Psychopharmacology 1998;138:107–13.

Steinpreis RE, Anders KA, Branda EM, Kruschel CK. The effects of atypical antipsychotics and phencyclidine (PCP) on rotorod performance. Pharmacol, Biochem Behav 1999;63:387–94.

Taylor GT. Affiliation and aggression in rats. Anim Learn Behav 1976;4: 139–44.

Vesce J, Comaty JE, Advokat C. Antiaggressive action of atypical antipsychotics in patients with schizophrenia. J Clin Psychopharmacol 2001; 21:353–5.

Volavka J. The effects of clozapine on aggression and substance abuse in schizophrenic patients. J Clin Psychiatry 1999;60:43–6.

Weddington WW. Cocaine: diagnosis and treatment. Psychiatr Clin North Am 1993;16:87–95.